Study on the anaphylactic shock induced by hemocoagulase for injection based on logistic analysis

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Abstract: In the present study, we aimed to explore the influencing factors of anaphylactic shock caused by hemocoagulase for injection and to provide a scientific basis for clinical safe medication. The cases reports on the adverse reactions induced by hemocoagulase for injection were collected in Chinese and foreign literatures. The clinical characteristics and influencing factors of anaphylactic shock induced by hemocoagulase for injection were evaluated by logistic regression analysis. In this study, 87 articles including 108 cases (68 cases of anaphylactic shock) were collected. Univariate logistic regression indicated that allergic constitution, daily dose, combined anesthesia, first drug delivery, post-dose time and course of treatment were positively associated with the incidence of anaphylactic shock caused by hemocoagulase for injection (P<0.05). The six above-mentioned factors were included in the multivariate logistic stepwise regression analysis to exclude the effects of confounding factors, and the results suggested that allergic constitution (P = 0.048, OR = 8.242), combined anesthesia (P = 0.024, OR = 22.675) and post-dose time (P = 0.006, OR = 20.255) were associated with the incidence of anaphylactic shock caused by hemocoagulase for injection. The clinicians should pay much more attention to risk factors that may cause anaphylactic shock, such as allergic constitution, combined anesthesia and post-dose time. The clinical pharmacists should strengthen pharmaceutical monitoring and improve the safety of medication.

Keywords: Hemocoagulase for injection; Logistic analysis; Anaphylactic shock

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1. Introduction

As a protease-type hemostatic drug extracted from snake venom, hemocoagulase has been extensively used in recent years due to its low toxicity, rapid and long lasting pesticide effect. Along with the frequent use of hemocoagulase for injection, the media coverage on the adverse drug reactions (ADR) is increasing gradually. Anaphylactic shock is the most serious ADR. Currently, the study on ADR of hemocoagulase mainly includes the case report and literature analysis. The case report is similar to descriptive analysis which only records the patients' general information, physiological factors and drug factors. Moreover, the literature analysis consists of systematic evaluation and review, along with the analysis of bibliometrics. However, there is still no systematic quantitative analysis of the influencing factors of adverse reactions caused by hemocoagulase. The application of binary logistic regression analysis method in influencing factors analysis of disease and outcome is relatively mature since the method can reflect the quantitative relation between each influencing factor and outcome. On the basis of the above-mentioned method, this assay conducts the study on signal of anaphylactic shock induced by hemocoagulase for injection by means of data retrieval of case reports on adverse reaction of hemocoagulase in Chinese and foreign literature database from 1990 to 2018. This research is of realistic significance which can provide reasonable

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medication advises to doctors so as to reduce the adverse reaction of hemocoagulase for injection.

2. Materials and methods

2.1. General data

The cases with ADR caused by hemocoagulase for injection were retrieved in CNKI, VIP, Wanfang and PubMed between 1990 and 2018 (updated September 2018). Full text retrieval search terms included: Hemocoagulase and ADR, Hemocoagulase adverse reaction. Inclusion criteria were as follows: ① Case report on ADR of hemocoagulase for injection; ② Detailed information of patients should be provided in the case report. Exclusion criteria were as follows: ① The cases lack any of the following information: gender, age, dose, route of administration and adverse reaction performance; ② Comprehensive literature analysis on ADR of hemocoagulase for injection.

2.2. Methods

The collected cases were summarized, and corresponding database was established through Office software. The related important factors in ADR report form were taken as the benchmark, and then the basic information was confirmed based on physiological factors and drug factors of patients. Cases database information included: first author, publication year, title, patient gender, age, allergic constitution, combination medication, daily dose, course of treatment, combined anesthesia (Y/N), first drug delivery (Y/N), post-dose time and course of treatment, perioperative administration of drug (Y/N), anaphylactic shock (Y/N), etc.

2.3. Data statistics and analysis

The SPSS 19.0 Software was used to analysis and statistics. The data were expressed as x±s. The enumeration data were expressed as %, and the χ^2 test was used for comparison between the two groups. The factors affecting anaphylactic shock induced by hemocoagulase for injection were screened by univariate logistic regression. Multivariate logistic stepwise regression analysis was performed to rule out the effect of confounding factors on the results. The test standard for the entry equation was 0.05, the deleting standard was 0.10, and $P<0.05$ was considered as statistically significant.

3. Results

3.1. Basic information

A total of 87 full-text articles were collected in this study. In total, 108 patients (68 in the anaphylatic shock group and 40 in the non-anaphylatic shock group) between 1 month and 78 years of age were enrolled. In the study, the mean age of patients was 47.43±19.44 years. The sex distribution (male to female) was 68 to 40. The symptomatic treatment was given immediately when there was the occurrence of ADR, and 105 were improved. However, three cases died of anaphylactic shock. Detailed retrieval process was shown in Figure 1. Comparison of the baseline data between the anaphylatic shock group and non-anaphylatic shock group was described in Table 1.

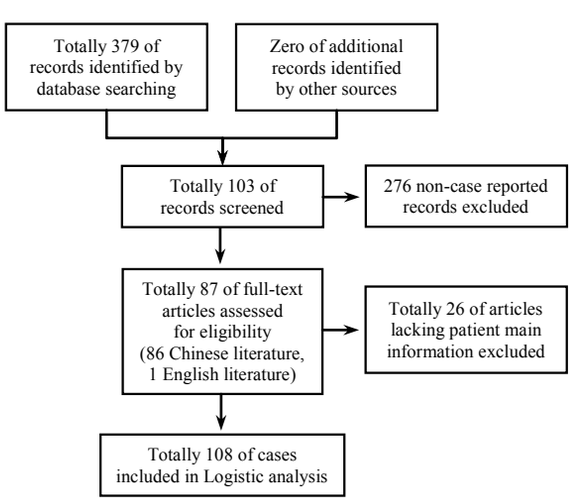

Figure 1. Document retrieval flow chart.

Table 1. Comparison of the baseline data between the anaphylatic shock group and non-anaphylatic shock group.

Variable	Non-anaphylatic shock (n = 38)	Anaphylatic shock (n = 70)	χ^2	P
Gender				
Female	16 (40.0%)	24 (60.0%)	0.239	0.625
Male	24 (35.3%)	44 (64.7%)		
Age (years)				
0–14	1 (2.5%)	6 (8.8%)		
15–64	30 (75.0%)	49 (72.1%)	1.966	0.374
≥65	9 (22.5%)	15 (19.1%)		
Allergic constitution				
No	11 (27.5%)	29 (42.6%)		
Yes	1 (2.5%)	17 (25.0%)	16.923	<0.0001
Unknown	26 (70.0)	22 (32.4%)		
Drug combination				
No	25 (62.5%)	45 (64.7%)	0.053	0.818
Yes	15 (37.5%)	25 (35.3%)		
First drug delivery				
No	12 (30.0%)	6 (8.8%)	8.132	0.004
Yes	28 (70.0%)	62 (91.2%)		
High daily dose*				
No	35 (87.5%)	67 (98.5%)	3.926	0.048
Yes	5 (12.5%)	1 (1.5%)		
Route of administration				
Intravenous injection	27 (67.5%)	49 (72.1%)		
Intramuscular injection	3 (7.5%)	4 (5.9%)	0.546	0.946
Intravenous infusion	7 (17.5%)	10 (14.7%)		
Others	3 (7.5%)	5 (7.4%)		
Course of treatment				
≤3 d	32 (80.0%)	67 (98.5%)	9.024	0.003
＞3 d	8 (20.0%)	1 (1.5%)		
Perioperative administration of drug				
No	14 (35.0%)	23 (33.8%)	0.015	0.901
Yes	26 (65.0%)	47 (66.2%)		
Combined anesthesia				
No	39 (97.5%)	54 (79.4%)	6.890	0.009
Yes	1 (2.5%)	14 (20.6%)		
Post-dose time				
1–10 min	28 (73.7%)	67 (95.7%)	11.289	0.001
≥11 min	10 (26.3%)	3 (4.3%)		

*Pediatric patients (0–14 years old) daily dose ≥2 IU, other patients daily dose ≥4 IU.

3.2. Factors assignment

Considering the clinical relevance, the factor assignment is shown in Table 2.

3.3. The results of univariate logistic regression analysis

Univariate logistic regression indicated that allergic constitution (P = 0.015, OR = 13.000), first drug delivery (P = 0.007, OR = 4.429), daily dose (P = 0.025, OR = 11.824), course of treatment (P = 0.009, OR = 16.750), combined anesthesia (P = 0.028, OR = 10.111) and post-dose time (P = 0.002, OR = 12.517) were associated with the incidence of anaphylactic shock caused by hemocoagulase for injection. It was described in Table 3. In combination with factor assignment (Table 2), we knew that the patients with allergic constitution, daily

Table 2. Factors assignment.

Factors	Name of variables	Assignment explanation
X_1	Gender	1 = Male, 0 = Female,
X_2	Age	2 = Age (≥65 years), 1 = Age (15–64 years), 0 = Age (0–14 years)
X_3	Allergic constitution	1 = Yes, 0 = Others
X_4	Drug combination	1 = Yes, 0 = No
X_5	First drug delivery	1 = Yes, 0 = No
X_6	Daily dose	1 = Pediatric patients (0–14 years old) (daily dose ≤2 IU, other patients daily dose ≤ 4 IU), 0 = Others
X_7	Route of administration	1 = Intravenous injection, 0 = Others
X_8	Course of treatment	2 = No more than 3 d (≤3 d), 1 = More than 3 d (>3d)
X_9	Perioperative administration of drug	1 = Yes, 2 = No
X_{10}	Combined anesthesia	1 = Yes, 2 = No
X_{11}	Post-dose time	2 = No more than 10 min (0–10 min), 1 = More than 10 min
Y	Anaphylactic shock	1 = Yes, 0 = No

Table 3. The results of univariate logistic regression analysis.

Independent variables	β	Wals	*P*	OR
Gender	0.201	0.239	0.625	1.222
Age[a]				
Age (0–14 years)	–1.301	1.387	0.239	0.272
Age (15–64 years)	–1.424	1.497	0.221	0.241
Allergic constitution	2.565	5.959	0.015[b]	13.000
Drug combination	–0.095	0.053	0.818	0.909
First drug delivery	–1.448	7.336	0.007[b]	4.429
Daily dose	2.470	5.038	0.025[b]	11.824
Route of administration	0.216	0.251	0.617	1.242
Course of treatment	2.818	6.782	0.009[b]	16.750
Perioperative administration of drug	0.052	0.015	0.901	1.054
Combined anesthesia	2.314	4.798	0.028[b]	10.111
Post-dose time	2.527	9.970	0.002[b]	12.517

Note: [a]Compared with age (≥65 years) group. [b]There was significant statistical difference.

dose (0–14 years old pediatric patients daily dose ≤2 IU and other patients daily dose≤4 IU), course of treatment (≤3 d), first drug delivery, combined anesthesia and post-dose time (≤10 min) were associated with an increased hazard of anaphylactic shock.

3.4. The results of multivariate logistic stepwise regression analysis

Multivariate logistic stepwise regression was used to analyze the six factors obtained by the above univariate logistic regression. The result was described in Table 4. It was shown that post-dose time (P = 0.006, OR = 20.255, 95% CI = 2.357–174.071), allergic constitution (P = 0.048, OR = 13.000, 95% CI = 1.017–66.799) and combined anesthesia (P = 0.024, OR = 22.675, 95% CI = 1.495–343.837) were independent risk factors of anaphylactic shock caused by hemocoagulase for injection. We could learn that the patients with allergic constitution, combined anesthesia and post-dose time (≤10 min) were significantly associated with an increased hazard of anaphylactic shock.

Table 4. The results of multivariate logistic stepwise regression analysis.

Independent variables	β	Wals	OR	95% CI	*P*
Post-dose time	3.008	7.514	20.255	2.357–174.071	0.006
Allergic constitution	2.109	3.904	8.242	1.017–66.799	0.048
Combined anesthesia	3.121	5.061	22.675	1.495–343.937	0.024

4. Discussion

4.1. More attention should be paid to the patient's allergy history or high-sensitivity constitution

Hemocoagulase is a thrombin-like enzyme extracted from snake venom. It is essentially a heterologous protein. On the one hand, it may become an allergen that causes allergic reactions. On the other hand, impurities may be introduced during the purification process, and the remaining venom enzymes or impurities may be an important cause of allergic reactions. The anaphylactic shock caused by hemocoagulase is closely related to whether the patient is allergic. In this study, 14 patients with anaphylactic shock had a history of drug, food or transfusion allergy, and three cases were hypersensitive (two cases bronchial asthma, one case Behcet's disease). Studies have shown that[1], asthma or other IgE-related diseases is significantly associated with an increased hazard of anaphylactic shock. If the patient is in an allergic state, there are IgE antibodies and a large amount of active inflammatory mediators, such as histamine, slow-acting state and leukotrienes, which may cause a more intense allergic reaction. The doctors need to pay more attention to the patient's allergy history or high-sensitivity constitution before prescribing,

4.2. More attention should be paid to patients with combined anesthesia

On the one hand, the anesthetic itself can cause anaphylactic shock. Neuromuscular blockers (NMBAS) are the most common drugs that cause perioperative allergies, including succinylcholine, rocuronium bromide, and cis-atracurium[2]. Propofol, fentanyl and lidocaine are also frequently reported[3,4]. Although the cases of anaphylactic shock caused by anesthetics were excluded in this study, anesthetics might increase the risk of anaphylactic shock by stimulating mast cells, basophils and other inflammatory mediators, such as histamine, prostaglandin D2 and white three[5]. On the other hand, patients with combined anesthesia recover more slowly from shock because of the inhibitory effects of anesthetics on the nerve center and cardiovascular. It is necessary to continuously pump vasoactive drugs for a period of time to maintain cycle stability[6].

4.3. Further study should be focused on monitoring the patient's condition within 10 min of post-dose time

In this study, 95.7% of the patients developed anaphylactic shock within 10 min after administration, and 3 of 68 patients with anaphylactic shock died. Medical staff should strengthen the monitoring the patient's condition within 10 min of post-dose time because anaphylactic shock is very urgent. The basic principle of first aid for anaphylactic shock is to stop the infusion of suspicious drugs, ensure airway patency, and maintain circulatory stability. Epinephrine is the drug of choice. When the venous access is not established, 0.01 mL/kg of epinephrine (concentration 1 mg/mL) should be intramuscularly injected in the deep thigh muscles, and the maximum dose should not exceed 0.5 mL[7].

4.4. Limitations of the study

Case series studies were not included in this study because of the lack of individual detailed information

on ADRs induced by hemocoagulase for injection. Because the number of cases in this study is small, the possibility of statistical shift can not be ruled out. Therefore, for the safety analysis of patients using hemocoagulase for injection, it is still necessary to collect large-scale clinical data for further study.

5. Conclusions

The clinicians should pay much more attention to risk factors that may cause anaphylactic shock, such as allergic constitution, combined anesthesia and post-dose time. The clinical pharmacists should strengthen pharmaceutical monitoring and improve the safety of medication.

References

[1] González-Pérez, A.; Aponte, Z.; Vidaurre, C.F.; Rodríguez, L.A.G. Anaphylaxis epidemiology in patients with and patients without asthma: a United Kingdom database review. *J. Allergy Clin. Immunol.* **2010**, *125*, 1098–1104.

[2] Dewachter, P.; Mouton-Faivre, C.; Castells, M.C.; Hepner, D.L. Anesthesia in the patient with multiple drug allergies: are all allergies the same? *Curr. Opin. Anesthesiol.* **2011**, *24*, 320–325.

[3] Belső, N.; Kui, R.; Szegesdi, I.; Kakuja, M.; Kapitany, K.; Kemeny, L.; Bata-Csörgő, Z. Propofol and fentanyl induced perioperative anaphylaxis. *Br. J. Anaesth.* **2011**, *106*, 283–284.

[4] Al-Dosary, K.; Al-Qahtani, A.; Alangari, A. Anaphylaxis to lidocaine with tolerance to articaine in a 12 year old girl. *Saudi Pharm. J.* **2014**, *22*, 280–282.

[5] Magnan, A.; Pipet, A.; Berard, F.; Malinovsky, J.M.; Mertes, P.M. Mechanisms of allergic reactions occurring during anaesthesia. *Ann. Fr. Anesth. Reanim.* **2011**, *30*, 240–245.

[6] Yang, R.Y.; Chen, H. Literature Analysis of Adverse Drug Reaction Induced by Haemocoagulase Agkistrodon. *Chin. J. Pharmacoepidemiol*. **2014**, *23*, 633–635.

[7] Muraro, A.; Roberts, G.; Worm, M.; Bilò, M.B.; Brockow, K.; Fernández Rivas, M.; Bindslev-Jensen, C. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy.* **2014**, *69*, 1026–1045.

基于logistic分析法的注射用血凝酶致过敏性休克研究

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摘要: 探讨注射用凝血酶致过敏性休克的影响因素, 为临床安全用药提供科学依据。本文通过检索收集中外文献中关于注射用血凝酶所致不良反应的病例报道, 对注射用血凝酶致过敏性休克的临床特点及影响因素进行Logistic回归统计分析。本研究共收集到87篇文献, 总计108个病例(过敏性休克病例68例)。单因素logistic回归分析结果显示: 过敏性体质, 日剂量, 首次给药, 合并麻醉, 给药后时间, 疗程与过敏性休克发生率呈明显相关(P<0.05)。将以上6个因素纳入logistic多因素逐步回归分析排除混杂因素影响, 结果显示: 过敏体质((P = 0.048, OR = 8.242), 合并麻醉 (P = 0.024, OR = 22.675), 给药后时间((P = 0.006, OR = 20.255)是注射用血凝酶发生过敏性休克的独立危险因素。结果发现, 临床医师应该注意注射用血凝酶致过敏性休克的高危因素如过敏体质、合并麻醉、用药后时间等。临床药师应注意加强药学监护提高用药安全性。

关键词: 注射用血凝酶; Logistic回归分析; 过敏性休克