

## Supplementary Materials

Defibrinogen Therapy for Acute Ischemic Stroke: 1332 Consecutive Cases

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#### Inclusion Criteria

- Age  $\geq$  18 years
- Signs and symptoms of ischemic stroke (any vascular territory)
- Within 72 hours after recognized symptom onset
- 5  $\leq$  Pretreatment NIHSS  $\leq$  22
- Initial fibrinogen level  $\geq$  1.5g/L
- Written informed consent

#### Exclusion Criteria

- Coma
- Large area of infarction lesion or multiple ischemic lesions
- Clinical or neuroimaging evidence of intracranial hemorrhage
- Obvious bleeding tendency or abnormal of blood platelet count or coagulation function disorders
- History of severe brain trauma or intracranial hemorrhage or digestive tract hemorrhage
- Exposure to defibrinogenating or snake venom agents within 1 week
- Use or intended use of thrombolytic agent
- Persistent systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg
- Associated severe primary disease of heart, liver, kidney or infectious diseases or hematological system or malignant tumor or severe progressive disease in any other system
- People with allergies or in pregnant

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Appendix 1. Selection criteria for patients receiving defibrinogen therapy.  
Abbreviations: SD, standard deviation; NIHSS, National Institute of Health Stroke Scale

|                                    | Pretreatment | At the 14 <sup>th</sup> day | t      |
|------------------------------------|--------------|-----------------------------|--------|
| <b>Hematology</b>                  |              |                             |        |
| Plasma viscosity, mPa/s, mean (SD) | 1.7 (0.13)   | 1.3 (0.12)                  | 67.62* |
| Hct value, %                       | 46.4 (0.09)  | 42.2 (0.06)                 | 14.14* |
| Platelet aggregation rate, %       | 65.9 (12.4)  | 57 (12.4)                   | 17.89* |
| PLT, $\times 10^9/L$ , mean (SD)   | 224 (61.4)   | 210 (60.3)                  | 5.76*  |
| Hemoglobin, g/L, mean (SD)         | 141 (21.9)   | 138 (16.3)                  | 3.65*  |
| <b>Coagulation Function</b>        |              |                             |        |
| APTT, s, mean (SD)                 | 34.8 (5.1)   | 26.3 (3.8)                  | 49.04* |
| PT, s, mean (SD)                   | 12.7 (3.9)   | 11.9 (4.1)                  | 4.77*  |
| TT, s, mean (SD)                   | 19.6 (2.4)   | 16.3 (2.3)                  | 36.51* |

Appendix 2. Hematology and coagulation function parameters pretreatment and at the 14<sup>th</sup> day after admission. \* The corresponding *P* value is less than 0.001 by paired samples *t* test. Abbreviations: SD=standard deviation, Hct=Hematocrit value, PLT=Platelet count, APTT=activated partial thromboplastin time, PT=prothrombin time, TT=thrombin time

|                                          | 3 months      |                    |          | 12 months     |                   |          |
|------------------------------------------|---------------|--------------------|----------|---------------|-------------------|----------|
|                                          | Loss (n= 156) | Not loss (n= 1164) | <i>P</i> | Loss (n= 203) | Not loss (n= 884) | <i>P</i> |
| Age, year                                |               |                    | 0.783    |               |                   | 0.309    |
| ≤ 60, n (%)                              | 50(32.1)      | 368(31.6)          |          | 72(35.5)      | 274(31.0)         |          |
| 61-79, n (%)                             | 87(55.8)      | 674(57.9)          |          | 114(56.2)     | 511(57.8)         |          |
| ≥ 80, n (%)                              | 19(12.2)      | 122(10.5)          |          | 17(8.4)       | 99(11.2)          |          |
| Male, n (%)                              | 85(54.5)      | 645(55.4)          | 0.827    | 106(52.2)     | 483(54.6)         | 0.532    |
| Smoking, n (%)                           | 44(28.2)      | 384(33.0)          | 0.231    | 63 (31.0)     | 281(31.8)         | 0.835    |
| Hypertension, n (%)                      | 81(51.9)      | 643(55.2)          | 0.612    | 103(50.7)     | 487(55.1)         | 0.262    |
| Diabetes mellitus, n (%)                 | 61(39.1)      | 430(36.9)          | 0.600    | 77(37.9)      | 320(36.2)         | 0.644    |
| Atrial fibrillation, n (%)               | 36(23.1)      | 308(26.5)          | 0.366    | 56(27.6)      | 229(25.9)         | 0.623    |
| Dyslipidemia, n (%)                      | 46(29.5)      | 339(29.1)          | 0.925    | 56(27.6)      | 259(29.3)         | 0.628    |
| Plasma viscosity, mPa/s, mean (SD)       | 1.71(0.14)    | 1.70(0.12)         | 0.477    | 1.69(0.12)    | 1.70(0.13)        | 0.760    |
| Hct value, %                             | 0.46(0.07)    | 0.47(0.10)         | 0.401    | 0.47(0.11)    | 0.46(0.09)        | 0.661    |
| Platelet aggregation rate, %             | 67.45(13.04)  | 65.65(12.38)       | 0.091    | 64.64(13.23)  | 65.89(12.02)      | 0.192    |
| PLT, ×10 <sup>9</sup> /L, mean (SD)      | 218(60.81)    | 224(61.35)         | 0.198    | 229.22(63.11) | 224.95(60.92)     | 0.371    |
| Hemoglobin, g/L, mean (SD)               | 142.27(24.78) | 141.33(21.42)      | 0.613    | 141.55(15.19) | 141.25 (21.83)    | 0.851    |
| APTT, s, mean (SD)                       | 35.04(4.78)   | 34.83(5.17)        | 0.634    | 35.28(4.70)   | 34.75(5.27)       | 0.198    |
| PT, s, mean (SD)                         | 12.76(2.62)   | 12.73(4.02)        | 0.913    | 12.72(1.82)   | 12.78(4.63)       | 0.839    |
| TT, s, mean (SD)                         | 20.03(2.51)   | 19.60(2.39)        | 0.630    | 19.65(2.31)   | 19.62(2.39)       | 0.860    |
| History of prior TIA, n (%)              | 22(14.1)      | 205(17.6)          | 0.275    | 34(16.7)      | 157(17.8)         | 0.733    |
| History of prior stroke, n (%)           | 23(14.7)      | 171(14.7)          | 0.986    | 22(10.8)      | 134(15.2)         | 0.113    |
| Blood pressure, mmHg,                    | 158.67(13.29) | 157.52(12.34)      | 0.279    | 158.01(12.24) | 157.31(12.48)     | 0.472    |
|                                          | /89.10(7.75)  | /88.31(8.22)       | /0.308   | /88.33(8.73)  | /88.26(8.18)      | /0.908   |
| Pretreatment NIHSS                       |               |                    | 0.171    |               |                   | 0.629    |
| 5-7, n (%)                               | 56(35.9)      | 334(28.7)          |          | 55(27.1)      | 253(28.6)         |          |
| 8-15, n (%)                              | 73(46.8)      | 619(53.2)          |          | 115(56.7)     | 469(53.1)         |          |
| ≥ 16, n (%)                              | 27(17.3)      | 211(18.1)          |          | 33(16.3)      | 162(18.3)         |          |
| Time to treatment, h                     |               |                    | 0.777    |               |                   | 0.771    |
| ≤ 6, n (%)                               | 9(5.8)        | 84(7.2)            |          | 14(6.9)       | 62(7.0)           |          |
| 7-12, n (%)                              | 18(11.5)      | 144(12.4)          |          | 22(10.8)      | 115(13.0)         |          |
| 12-24, n (%)                             | 31(19.9)      | 187(16.1)          |          | 31(15.3)      | 144(16.3)         |          |
| 25-48, n (%)                             | 51(32.7)      | 397(34.1)          |          | 67(33.0)      | 301(34)           |          |
| 49-72, n (%)                             | 47(30.1)      | 352(30.2)          |          | 69(34.0)      | 262(29.6)         |          |
| Initial fibrinogen level, g/L, mean (SD) | 3.15(0.95)    | 3.19(1.06)         | 0.692    | 3.27(1.15)    | 3.16(1.01)        | 0.165    |
| Initial BI, mean (SD)                    | 52.08(13.14)  | 52.41(13.25)       | 0.769    | 51.86(13.60)  | 52.96(13.05)      | 0.072    |
| Modified Rankin Score                    |               |                    | 0.205    |               |                   | 0.601    |
| 2 or 3, n (%)                            | 55(35.2)      | 341(29.3)          |          | 67(33.0)      | 257(29.1)         |          |
| 4 or 5, n (%)                            | 101(64.7)     | 823(70.7)          |          | 136(67.0)     | 595(67.3)         |          |
| Number of defibrase infusions            |               |                    | 0.301    |               |                   | 0.545    |
| 1, n (%)                                 | 17(10.9)      | 178(15.3)          |          | 27(13.3)      | 138(15.6)         |          |
| 2, n (%)                                 | 22(14.1)      | 174(14.9)          |          | 34(16.7)      | 127(14.4)         |          |
| 3, n (%)                                 | 117(75.0)     | 812(69.8)          |          | 142(70.0)     | 619(70.0)         |          |

|                   |          |           |          |           |       |
|-------------------|----------|-----------|----------|-----------|-------|
| Dose of defibrase |          |           | 0.108    |           | 0.080 |
| 5 U, n (%)        | 4(2.6)   | 67(5.8)   | 8(3.9)   | 52(5.9)   |       |
| 10 U, n (%)       | 21(13.5) | 131(11.3) | 17(8.4)  | 109(12.3) |       |
| 15 U, n (%)       | 33(21.2) | 189(16.2) | 39(19.2) | 136(15.4) |       |
| 20 U, n (%)       | 57(36.5) | 372(32.0) | 78(38.4) | 269(30.4) |       |
| 25 U, n (%)       | 29(18.6) | 292(25.1) | 44(21.7) | 228(25.8) |       |
| 30 U, n (%)       | 12(7.7)  | 113(9.7)  | 17(8.4)  | 90(10.2)  |       |

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Appendix 3 Differences between the patients of loss to follow-up and patients of being followed up at 3 months and 12 months of demographic and baseline clinical characteristics. Abbreviations: SD, standard deviation; Hct=Hematocrit value, PLT=Platelet count, APTT=activated partial thromboplastin time, PT=prothrombin time, TT=thrombin time; TIA = transient ischemic attack; NIHSS, National Institute of Health Stroke Scale

|                            | Barthel Index (95 or 100) |                | mRS (0 or 1)   |                |
|----------------------------|---------------------------|----------------|----------------|----------------|
|                            | 3months                   | 12 months      | 3months        | 12 months      |
| Initial fibrinogen, n/N, % |                           |                |                |                |
| 1.5-2.0 g/L                | 45/96, 46.9               | 33/66, 50.0    | 26/96, 26.1    | 33/66, 50.0    |
| ≥ 2.0 g/L                  | 481/991, 48.5             | 425/708, 60    | 391/991, 39.5* | 424/708, 59.9  |
| Times of defibrase, n/N, % |                           |                |                |                |
| Once                       | 75/166, 45.2              | 67/119, 56.3   | 48/166, 41.5   | 67/119, 46.3   |
| Twice                      | 87/171, 50.99             | 76/120, 63.3   | 71/171, 41.5   | 77/120, 64.1   |
| Three times                | 364/750, 48.5             | 315/535, 58.9  | 277/750, 36.9* | 314/536, 58.6  |
| Dose of defibrase, n/N, %  |                           |                |                |                |
| 5U                         | 29/81, 35.8               | 31/58, 53.4    | 51/81, 63.0    | 40/58, 69.0    |
| 10U                        | 60/108, 55.6              | 51/81, 63.0    | 20/108, 18.5   | 36/81, 44.4    |
| 15 U                       | 74/165, 44.8              | 89/122, 73.0   | 42/165, 25.5   | 86/122, 70.5   |
| 20 U                       | 187/345, 54.2             | 150/232, 64.7  | 147/345, 42.6  | 110/232, 47.4  |
| 25 U                       | 130/294, 44.2             | 111/219, 50.7  | 141/294, 48.0  | 122/219, 55.7  |
| 30 U                       | 47/94, 50.0**             | 34/64, 53.1**  | 17/94, 18.1**  | 16/64, 25**    |
| Time-to-treat, n/N, %      |                           |                |                |                |
| 0-6h                       | 37/78, 47.44              | 33/52, 63.46   | 31/78, 39.74   | 23/52, 44.23   |
| 7-12h                      | 64/134, 47.76             | 59/102, 57.84  | 61/134, 45.52  | 66/102, 64.71  |
| 13-24h                     | 80/178, 44.94             | 78/128, 60.94  | 68/178, 38.20  | 71/128, 55.47  |
| 25-48h                     | 184/366, 50.27            | 159/264, 60.23 | 138/366, 37.70 | 162/264, 61.36 |
| 49-72h                     | 161/331, 48.64            | 129/229, 56.33 | 119/331, 35.95 | 136/229, 59.39 |

Appendix 4. Distribution by percent of patients attained Functional success in different categories; N, the total number of patients followed up at 3months or 12 months; \*,  $P < 0.05$ ; \*\*,  $P < 0.01$ . Abbreviations: mRS=modified Rankin Score