

The timing of symptomatic pulmonary embolism in patients with non-warfarin following elective primary total joint arthroplasty

CHUAN HU

affiliated hospital of qingdao university <https://orcid.org/0000-0002-4887-4079>

CHUAN LIU

first hospital of china medical university

YUAN-HE WANG

affiliated hospital of qingdao university

TAO DING

affiliated hospital of weifang medical university

KANG SUN

affiliated hospital of qingdao university

XU YANG

affiliated hospital of qingdao university

GUO-BO ZENG

people's hospital of xixiu district

Shao-qi TIAN (✉ shaoqi99@aliyun.com)

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Abstract

Background: The purpose of this study was to investigate the incidence and timing of postoperative symptomatic pulmonary embolism (PE) in patients receiving non-warfarin following primary total joint arthroplasty (TJA), to clarify the appropriate duration of postoperative VTE prophylaxis.

Methods: We retrospectively reviewed the medical records of 11148 patients who underwent primary TJA, including total knee arthroplasty (TKA) and total hip arthroplasty (THA) at our institution from January 2012 to March 2019. The median postoperative day of diagnosis of symptomatic PE and interquartile range for day of diagnosis were determined. Multivariate Cox proportional hazards modeling was used to test the difference of timing for PE based on demographics and comorbidities.

Results: The overall 90-day rate of symptomatic PE was 0.71%. The median day of diagnosis for symptomatic PE was 3 day postoperatively (interquartile: 2–7 day). Factors that showed statistical significance on multivariate analysis in association with earlier timing of PE occurrence in patients with atrial fibrillation, diabetes mellitus, coronary heart disease and history of stroke.

Conclusion: The vast majority symptomatic PE occurs in the early postoperative period after TJA, and atrial fibrillation, diabetes mellitus, coronary heart disease and history of stroke were independent factors affecting the timing of symptomatic PE.

Background

Total joint arthroplasty (TJA) is a cost-effective procedure for articular diseases such as osteoarthritis (OA), rheumatoid arthritis (RA) and avascular necrosis of the femoral head (ANFH). As the global population ages, the number of TJA is increasing and will continue to grow. According to the latest data, the number of total knee arthroplasty (TKA) and total hip arthroplasty (THA) in the United States will reach 635,000 and 1260000 procedures in 2030, respectively[1]. Although satisfactory effects can be obtained in most patients after TJA, some patients suffer serious complications, such as pulmonary embolism (PE), periprosthetic joint infection and periprosthetic fractures. This is still a serious challenge for orthopedic surgeons.

PE is one of the rare but devastating complications after TJA. The mortality rate is extremely high, which will lead to a serious economic burden to the society. Although various preventive measures (including physical prophylaxis and chemical prophylaxis, etc.) have been used in practice, the incidence of PE after arthroplasty is still between 0.2%–0.4%, which has not shown the decline in recent years[2–6]. Chemical prophylaxis is an important measure to prevent thrombosis after TJA, and warfarin, low molecular weight heparin (LMWH), rivaroxaban and aspirin are important chemical prophylaxis for venous thromboembolism following TJA. However, adverse effects caused by drugs, such as bleeding and ecchymoma, are problems that people attach great importance to. Therefore, it is very important to decide the appropriate duration of prophylaxis to find the best equilibrium point between venous thromboembolism (VTE) and adverse effects.

The current guidelines recommend a minimum of 10–14 days for chemical prophylaxis after joint arthroplasty, up to a maximum of 35 days. However, which did not classify the duration of different drugs[7]. Parvizi et al[8] have investigated the timing of symptomatic PE in patients with warfarin following arthroplasty and found that the median time of symptomatic PE after arthroplasty was 2 (range: 1–87) days postoperatively. Out of 283 documented symptomatic PE cases, 81 % of patients occurred within 3 days postoperatively, and 89% of patients occurred within 1 week postoperatively. However, the clinical administration to anticoagulant therapy has changed recently due to several limitations of warfarin, including slow onset and offset of effect, a narrow therapeutic window, and variable dose-response relations, which necessitate frequent monitoring using International Normalized Ratio (INR) and dose adjustments[9]. Therefore, many countries selected LMWH, rivaroxaban or aspirin as the main methods of VTE prophylaxis after major orthopedic surgery, while warfarin was rarely used[10, 11]. However, few studies have focused on the timing distribution of postoperative symptomatic PE in patients with non-warfarin prevention. Therefore, the purpose of this study was to investigate the incidence and timing of postoperative symptomatic PE in patients with non-warfarin following TJA, to clarify the appropriate duration of postoperative VTE prophylaxis.

Methods

Participants

We retrospectively review the medical records of 11148 patients who underwent TKA or THA in the Department of Orthopedic, The Affiliated Hospital of Qingdao University from January 2012 to March 2019. 373 patients were excluded due to 63 patients without complete follow-up information or hospitalization data, 211 patients underwent revision arthroplasty, 48 patients with confirmed VTE preoperatively, 25 patients with the previous history of PE, 18 patients with coagulopathy, and 8 patients with age less than 18 years. Finally, 10775 patients were included in this study, including 7381 patients underwent primary TKA, 3371 patients underwent primary THA, and 23 patients underwent primary TKA and primary THA during a single surgical procedure. Demographics, comorbidities, inpatient medical records and 90-day follow-up data for all patients will be extracted and analyzed.

Management of Patients

Patients were enrolled to complete electrocardiogram (ECG), laboratory examination and imaging examinations after admission. For patients with articular fractures or VTE high-risk patients, Color Doppler ultrasound was performed to exclude deep vein thrombosis (DVT), and patients diagnosed with DVT preoperatively will be excluded from the study. All patients used tranexamic acid as the hemostatic, which was intravenous application before skin incision in THA patients or before the tourniquet was inflated in TKA patients. In patients underwent THA procedure, the drainage tube was not used routinely. However, in patients underwent TKA procedure, the drainage tube was used routinely. If there were no special conditions, the drainage tube was removed within 24 hours after surgery. All patients were given

4100 IU of Low Molecular Weight Heparin Calcium or 4250 Low Molecular Weight Heparin Sodium subcutaneously after anesthesia on the surgery day. From the first day after surgery, all patients were given 4100 IU of Low Molecular Weight Heparin Calcium or 4250 Low Molecular Weight Heparin Sodium daily for subcutaneous injection and continued to be discharged. After the drainage tube was removed, all patients received rehabilitation exercises and get out of bed for gait rehabilitation. After the patient was discharged from the hospital, aspirin or rivaroxaban were used for continuous anticoagulant therapy, and the medication lasted until 1 month after surgery.

Assessment of PE

All patients were not routinely examined for PE after the operation, such as CT pulmonary angiography (CTPA). CTPA was performed to diagnose PE when patients presented with clinical symptoms suspected of PE, such as dyspnea, chest pain, chest tightness, and hemoptysis. All patients with PE which was confirmed by CTPA were categorized into the PE group; but patients with suspected PE but not confirmed by the examination were not categorized into the PE group. The timing of PE is based on the time of the first symptom occurs, but not the auxiliary examination to confirm the PE as the time point at which PE occurs.

Statistical analysis

The incidence and timing of postoperative PE were described by percentage and median (interquartile range). Continuous variables were tested for normality using the Kolmogorov-Smirnov test firstly. Age, operative time, CCI, and BMI were tested between PE patients and Non-PE patients for statistical significance using Student's t-test or a Mann-Whitney U test depending on their distribution. categorical variables, such as gender and anesthesia, were analyzed using a Chi-squared test or Fisher's exact test as appropriate. Additionally, Cox regression was used to determine the association of demographics, procedures, and comorbidities with the timing of PE. All reported P values were 2 sided, and $P < 0.05$ was used to determine statistical significance. All analyses were performed using SPSS version 25.0 (IBM).

Results

10775 patients with primary THA or primary TKA who met the inclusion criteria of this study were included in the cohort, including 7381 patients underwent TKA, 3371 patients underwent THA, and 23 patients underwent primary TKA and primary THA during a single surgical procedure. Among the 10775 patients, including 3558 males and 7217 females, the average age of all patients was 64.52 ± 9.56 years. No fatal adverse events, such as PE and cardiac arrest, occurred intraoperatively among all patients. A total of 77 patients were diagnosed as symptomatic PE during the 90-days follow-up, and the incidence of symptomatic PE was 0.71%. Among the 77 symptomatic PE patients, 44 patients developed

symptomatic PE during hospitalization, and 33 patients developed symptomatic PE within 90 days of discharge. Among patients with symptomatic PE, 58 patients underwent TKA procedure and 19 patients underwent THA procedure, including 28 males and 49 females. Baseline and comorbidities are shown in Table 1.

The rate of patients with THA with symptomatic PE was 0.6% (19/3371), and the rate of patients with TKA with symptomatic PE was 0.8% (58/7381). There is no statistical significance between TKA and THA. In patients with symptomatic PE, the patient was older than patients without symptomatic PE (69.2 vs. 63.99, $P = 0.000$). In addition, patients with symptomatic PE were higher than those without symptomatic PE in the CCI scores. In preoperative comorbidities, the proportion of hypertension, coronary heart disease, atrial fibrillation, diabetes, and stroke in patients with symptomatic PE was significantly higher than patients without PE. Differences between the two groups were not statistically significant in terms of gender, BMI, alcohol and tobacco status, anesthesia, varicose veins, respiratory disease, and operative time. (Table.1) Incidence of fatal PE was 11.69% (9/77). Three cases of fatal PE occurred at postoperative day 1, one case occurred on day 3, four cases occurred on day 4, and one case occurred on day 7.

The median time at which PE occurred was 3 days postoperatively (interquartile range: 2–7 days). Of the 77 documented PE cases, 50.6% occurred within the first three postoperative days, 79.2% occurred within the first seven postoperative days, and only 6.5% of patients occurred after 30 days postoperatively (Figure.1). Factors that showed statistical significance on multivariate analysis in association with timing of PE included patients with or without atrial fibrillation ($P = 0.002$), CHD ($P = 0.000$), diabetes mellitus ($P = 0.002$), and history of stroke ($P = 0.009$) (Figure.2). However, there were no statistically significant differences in gender, age, BMI, CCI, anesthesia, operation time and other complications in the timing of symptomatic PE.

Discussion

The results of this study indicate that the median day for symptomatic PE in patients with non-warfarin following elective primary TJA was 3 (interquartile range: 2–7). Of the 77 documented symptomatic PE cases, 50.6% occurred within the first three postoperative days, 79.2% occurred within the first seven postoperative days, and only 6.5% of patients occurred in 30 days after surgery. Our results are consistent with the findings of recent research from Johnson et al and BOHL et al[12, 13]. Johnson et al[13] studied 1622 patients with PE after TJA based on the National Surgical Quality Improvement Program (NSQIP) database between 2011–2016, and indicated that the median day for PE following TJA was 3. BOHL et al[12] included 625 patients with PE after TJA from 2005 to 2013 based on the above database as well. The results showed that the median day of PE was 3 postoperatively (interquartile range: 2–7). However, none of the above studies described venous thromboembolism prophylaxis methods postoperative, so the targeted analysis was not possible. In addition, the patients of the above studies were followed up for 30 days. In our study, all of the patients were followed up to 90 days after surgery, which maximally completing data from patients with TJA-related PE.

Some investigators have studied the timing of VTE for specific venous thromboembolism prophylaxis methods previously. Parvizi et al[8] reported the incidence and timing of symptomatic PE in 283 TJA patients with warfarin following revision and primary TJA. The median time at which PE occurred was 2 days postoperatively (range: 1–87 days), and 89% cases occurred within the first postoperative week. Similarly, Parvizi et al[14] reported that patients following TJA who used warfarin as the methods for venous thromboembolism prophylaxis, and found that 75% of life-threatening medical complications occurred 1–2 days postoperatively.

Warfarin inhibits the gamma-carboxylation of glutamic acid residues of the vitamin K-dependent coagulation factors II, VII, IX, and X. This is the basis of the anticoagulation effect of this medication. The half-life of factors II, IX, and X is on the order of 60 hours. Therefore, the anticoagulation-effect of warfarin is somewhat delayed. Hence, patients with warfarin often have complications such as thrombosis and hemorrhage in the early stage[15–17]. In contrast, low molecular weight heparin or rivaroxaban usually reach peaks of blood concentration at 2–4 hours after administration[18–20], which may be one of the important reasons for the late onset of symptomatic PE in our research.

In summary, we can find that the early stage of postoperative surgery is a high-risk period of postoperative PE in patients following TJA, which is the result of a comprehensive effect of factors. Due to the effects of blood loss, the use of hemostatic and stress state, the patient's body often appears hypercoagulable condition postoperatively[21]. As we all know, hypercoagulability has been implicated in the pathogenesis of VTE events[22, 23]. previous studies have confirmed it, which found that 2–4 days after lower extremity arthroplasty was the peak of VTE [24, 25]. This may be one of the most important causes of PE usually occurring early in the postoperative period. In addition, the trigger also plays an important role in the occurrence of symptomatic PE. In the enhanced recovery after surgery (ERAS) management mode, patients with TJA are required to exercise during the early postoperative period. Previous studies have shown that patients with total knee arthroplasty have an upward trend in the first three days after surgery[26]. However, the first 2 days increased less than before, and the activity on the third day was significantly higher than that on the second day (About 2 times). All patients following THA in our institution do not routinely place drainage, and all patients were required to rehabilitate on the first day after surgery if possible. All patients following TKA placed one drainage and pull out it within 24 hours after surgery, and then carry out rehabilitation exercises. The level of rehabilitation exercise of all patients increases day by day, which may be an important trigger of early PE.

In this study, symptomatic PE occurred earlier in patients with atrial fibrillation when compared to patients without atrial fibrillation. Atrial fibrillation is one of the most important risk factors of VTE[27–29], which also has an important influence on the timing of PE after arthroplasty[8]. Previous studies have confirmed that the levels of fibrinogen, factor VIII and D-dimer in peripheral blood of patients with atrial fibrillation were significantly increased, while the levels of anticoagulant factor III, protein C and protein S were significantly decreased. This hypercoagulable state occurs with the occurrence of atrial fibrillation and is an important factor in promoting thrombosis[30, 31]. Additionally, symptomatic PE occurred earlier in patients with diabetes mellitus when compared to patients without diabetes mellitus. The association

between diabetes mellitus and VTE has been confirmed in a lot of literatures[32–34]. It may be related to hyperglycemia, which can be related to the enhancement of blood coagulation function by damaging vascular endothelial cells[35, 36]. We also find that symptomatic PE occurred earlier in patients with CHD or history of stroke when compared to patients without it. These patients have limited activity and braking, while the disease itself causes hypercoagulability of the blood, and often combined with hypoxia leads to hyperfunction of platelets and leukocytes, and then the coagulation mechanism is initiated. Causes chronic consumption of clotting factors, making these patients more prone to PE after surgery.

Our study has some limitations. First, although 77 patients were diagnosed as symptomatic PE, we cannot distinguish the components of embolus, such as thromboembolism, fat embolism and even air embolism, which may have a certain influence on the incidence and time distribution of PE in our study. However, considering the incidence of fat embolism and air embolism in patients following TJA was extremely low, we believed that the results of this study are highly reliable. Second, our study was limited to the evaluation of symptomatic PEs. We may have missed subclinical PE patients in asymptomatic patients. However, we felt that it would have not been possible or medically appropriate to screen all patients for PE. Finally, the number of patients was small. Nevertheless, our finding suggests that PE is an early event in patients receive non-warfarin following primary TJA.

Conclusion

This study indicates that in non-warfarin anticoagulant mode, the median time to symptomatic PE after TJA was 3 days postoperatively. Patients with atrial fibrillation, diabetes mellitus, coronary heart disease, or history of stroke are more likely to develop symptomatic PE earlier when compared to patients without it.

Abbreviations

PE: Pulmonary embolism; TJA: Total joint arthroplasty; TKA: Total knee arthroplasty; THA: Total hip arthroplasty; OA: Osteoarthritis; RA: Rheumatoid arthritis; ANFH: Avascular necrosis of the femoral head; LMWH: Low molecular weight heparin; VTE: Venous thromboembolism; INR: International normalized ratio; ECG: Electrocardiogram; DVT: Deep vein thrombosis; CTPA: CT pulmonary angiography; NSQIP: National surgical quality improvement program; ERAS: Enhanced recovery after surgery

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the affiliated hospital of Qingdao University. Written informed consent was obtained from all patients. No children (under 16 years old) were included in this study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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We received no external funding for this study.

Authors' Contributions

C H, S Q T, G B Z, T D, X Y and K S made substantial contributions to the design of this study, acquisition of data; C H, C L and Y H W analyzed the data; C H wrote the manuscript; All authors read and approved the final manuscript.

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Authors' information

1. Department of Orthopaedic Surgery, the Affiliated Hospital of Qingdao University, Qingdao, 266071, China
2. Department of Medical Oncology, the First Hospital of China Medical University, Shenyang, 110001, China
3. Department of Orthopaedic Surgery, the Affiliated hospital of Weifang Medical University, Weifang, 261031, China

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Tables

Table 1: Comparison between Patients With and Without PE.

Variable	Non-PE n=10698	PE n=77	t/c	p
Age	63.99±9.56	69.20±7.96	4.774	0.000
Gender			0.392	0.531
Male	3530	28		
Female	7168	49		
BMI	26.45±3.98	27.04±4.29	1.282	0.200
CCI	2.43±1.27	3.44±1.14	6.946	0.000
Smoking habits	1659	11	0.087	0.768
Drinking habits	1682	13	0.078	0.780
Procedure			1.776	0.412
THA	3352	19		
TKA	7323	58		
TKA+THA	23	0		
Anesthesia			1.340	0.247
General	6795	44		
Local	3903	33		
Operative time	90.00±33.87	94.17±31.83	1.077	0.281
Comorbidities				
Hypertension	4606	47	10.856	0.001
Coronary heart disease	1135	22	25.734	0.000
Atrial fibrillation	87	4	17.526	0.004
Diabetes mellitus	1418	23	18.218	0.000
Varicose veins	146	3	1.976	0.160
History of stroke	740	14	14.906	0.000
Respiratory disease	165	2	0.081	0.777

Figures

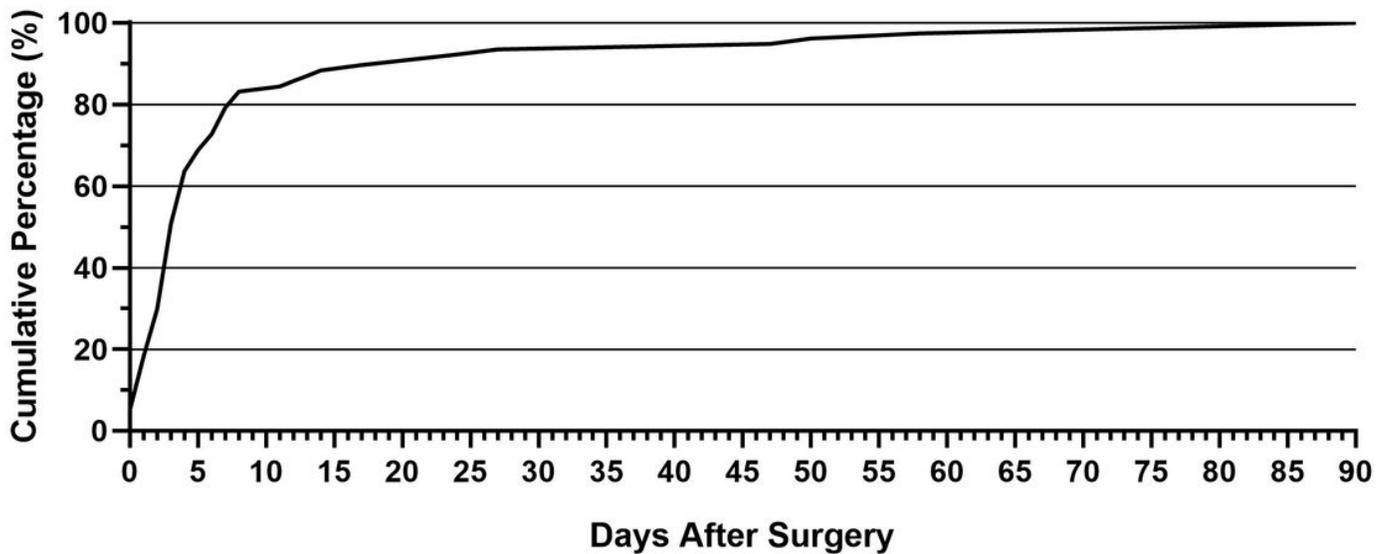


Figure 1

The figure shows that the timing distribution of PE in patients with non-warfarin following elective primary total joint arthroplasty. Of the 77 documented PE patients, 50.6% cases occurred within the first three postoperative days, 79.2% cases occurred within the first seven postoperative days, and only 6.5% cases occurred after 30 days postoperatively.

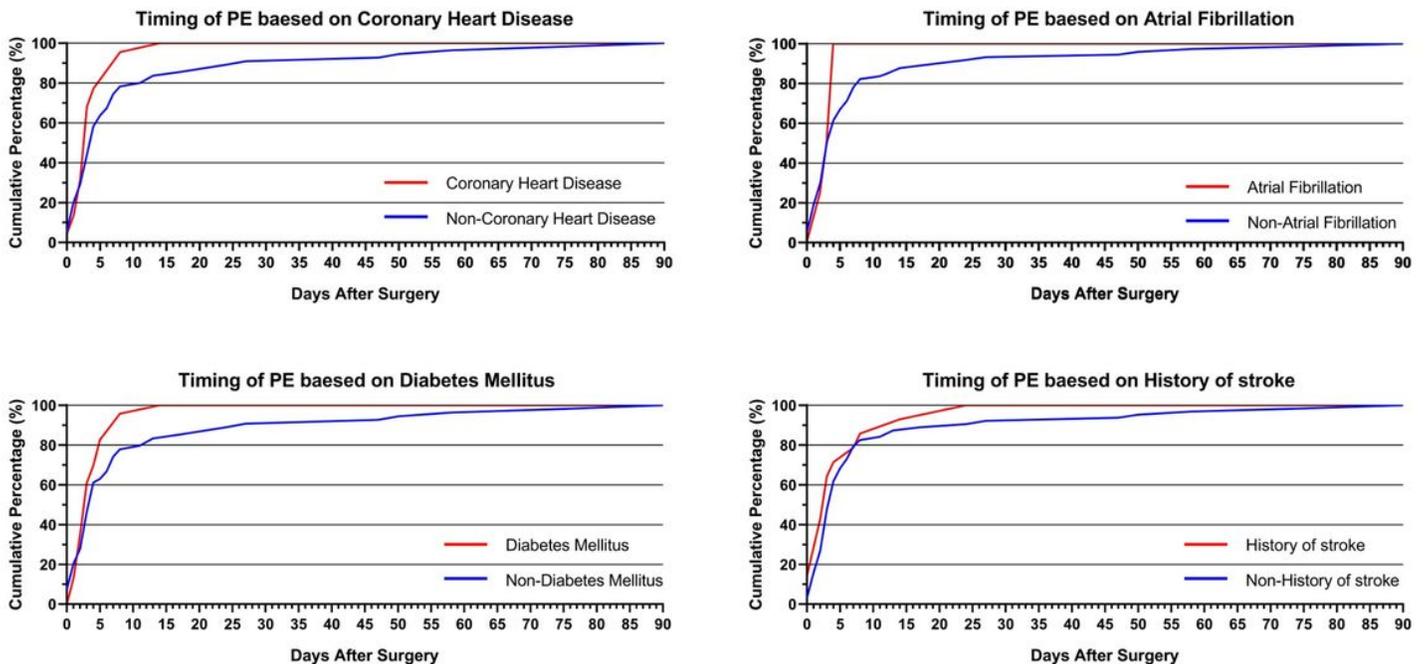


Figure 2

The figure shows that the timing curves of PE based on atrial fibrillation, CHD, diabetes mellitus, and history of stroke. Statistical analysis showed that atrial fibrillation, CHD, diabetes mellitus, and history of

stroke are factors influence the timing of PE (All P value < 0.05). Patients with atrial fibrillation, CHD, diabetes mellitus, or history of stroke tend to have earlier PE than patients without it.

Supplementary Files

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- [RAWDATA.sav](#)