Postoperative Myocardial Injury and Inflammation Is Not Blunted by a Trial of Atorvastatin in Orthopedic Surgery Patients

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Abstract *Background:* Orthopedic patients are at risk for adverse postoperative cardiovascular outcomes. *Questions/Purposes:* This pilot randomized controlled trial (RCT) of atorvastatin vs. placebo in orthopedic surgery patients was performed in order to assess: (1) the prevalence of perioperative myocardial injury; (2) the effect of atorvastatin on perioperative inflammation; and (3) the feasibility of performing a large RCT of statin therapy in orthopedic patients. *Methods:* Hip fracture (hip Fx) and total hip and knee replacement (THR and TKR) patients were randomized 1:1 to atorvastatin 40 mg daily vs. placebo, starting preoperatively and continuing until

postoperative day (POD) 45. High-sensitivity cardiac troponin I (hs-cTnI), high-sensitivity C-reactive protein (hs-CRP), and interleukin-6 (IL-6) were measured preoperatively and on POD 2. Patients were monitored for adverse events until POD 90. *Results:* Five hundred fifty-six patients were screened, 22 were recruited (4 hip Fx, 11 THR, 7 TKR), and 2 withdrew. Most (80%) had detectable hs-cTnI (> 1.1 pg/mL) preoperatively. Twenty percent had a perioperative rise in hs-cTnI (≥ 10 pg/mL), which was not blunted by atorvastatin. Hs-CRP rose in 19/20 patients, and IL-6 rose in all patients. However, atorvastatin did not blunt the rise in these inflammatory biomarkers.

Level of evidence: double-blind, randomized controlled trial, level II

The work was performed at Hospital for Special Surgery, New York Presbyterian Hospital, University of Utah (cytokine assays) and Washington University in St. Louis (hs-troponin and hs-CRP assays).

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On POD 2, IL-6 and hs-cTnI levels correlated ($\rho = 0.59$, $p = 0.02$). Recruitment was limited by the high prevalence of statin use in the screened population and a high prevalence of exclusions among hip fracture patients. *Conclusion:* Perioperative myocardial injury and inflammation are common in orthopedic patients and do not appear to be reduced in those randomized to atorvastatin. *Trial Registration:* NCT02197065

Keywords troponin · orthopedics · inflammation · interleukin-6 · C-reactive protein · myocardial ischemia

Introduction

Orthopedic patients are at risk for adverse postoperative cardiovascular (CV) outcomes. In the 6 months after hip fracture surgery, myocardial infarction (MI) occurs in 1.9–3.1% of patients [17] and death in 2.6–9.8% [17, 20, 23, 32]. Following hip and knee replacement, MI occurs in 0.2–0.5% [24, 27, 36], stroke in up to 0.2% [22, 30, 36], and death in 0.1–1.4% [22, 24, 36]. Myocardial infarction is in fact the most common cause of death after arthroplasty [5, 21]. Previously, we demonstrated elevated postoperative high-sensitivity cardiac troponin T levels in 13.5% of hip and knee replacement patients using an assay with a lower limit of detection of 13 pg/mL [3]. Others have shown that orthopedic surgery patients with a postoperative elevation in high-sensitivity troponin triple their long-term risk of mortality (16.8 vs. 5.8%) [33].

Three (3)-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors (“statins”) reduce the risk of adverse CV outcomes in patients with and without established heart disease [37, 40, 44]. They also reduce adverse CV outcomes following cardiac and vascular surgery [10, 42, 50] even when they are started only 1 day preoperatively [50]. Observational studies suggested that perioperative statins may reduce the risk of adverse CV outcomes in patients undergoing major non-cardiac surgery [6, 26], but this has not been demonstrated prospectively. Statins’ anti-inflammatory effects help protect against adverse CV outcomes, independent of their effects on lipids [35, 37]. Statins may also reduce the risk of venous thromboembolism [14] via anti-inflammatory effects such as suppression of interleukin-6 [1, 38].

Given that an excessive postoperative rise in interleukin-6 (IL-6) and other inflammatory markers is associated with complications of orthopedic surgery [46], perioperative administration of a statin may be beneficial. To explore this hypothesis, we conducted a pilot randomized controlled trial (RCT) of atorvastatin vs. placebo in patients undergoing orthopedic surgery. The primary aims of the study were the following: (1) to assess the prevalence of postoperative myocardial injury, as measured by a rise in serum high-sensitivity cardiac troponin I (hs-cTnI) from baseline to postoperative day (POD) 2; (2) to estimate the effect of atorvastatin 40 mg daily on change in serum high-sensitivity C-reactive protein (hs-CRP) levels from baseline to POD 2; and (3) to determine the feasibility of performing a large RCT of statin therapy in orthopedic patients. Secondary measures were the following: (1) the change in serum hs-cTnI level from baseline to POD 2 in patients randomized to atorvastatin 40 mg vs. placebo; (2) the change in the levels of IL-6 from

baseline to POD 2 in total hip or knee replacement (THR and TKR) patients randomized to atorvastatin 40 mg vs. placebo; and (3) the frequency of a composite cardiovascular outcome [myocardial infarction, stroke or transient ischemic attack, atrial fibrillation, or death] during the first 90 days after surgery.

Patients and Methods

This was a prospective, randomized, double-blind, placebo-controlled pilot trial (RCT; level II evidence, given the small sample size). Patients undergoing hip fracture (hip Fx) surgery and THR or TKR were randomized 1:1 to receive atorvastatin 40 mg daily or placebo. Randomization was stratified by surgery type and performed in blocks of 6 hip Fx or 4 THR and TKR. Randomization tables were generated by the study biostatistician and provided directly to investigational pharmacists at New York Presbyterian Hospital (NYPH) and Hospital for Special Surgery (HSS). All other study personnel and all patients were blinded to treatment assignment until completion of the trial.

For inclusion, we included patients ages ≥ 65 years, admitted for hip Fx surgery, or elective unilateral primary THR or TKR for osteoarthritis, with a life expectancy of > 3 months, who were able to speak English and participate in the informed consent process. The trial was initially designed to enroll hip Fx patients exclusively, but enrollment was expanded to THR and TKR patients in March 2015 to increase recruitment. We excluded patients who had taken a statin within the previous 30 days or were intolerant of statins, patients with a pathologic hip fracture, coronary artery disease, muscle disorder, liver disease, creatinine clearance < 30 cm³/min, treatment with an HIV protease inhibitor, hepatitis C protease inhibitor, erythromycin, clarithromycin, niacin, or an azole antifungal agent. We also excluded hip Fx patients if they had a history of peripheral arterial disease, transient ischemic attack, or stroke.

Hip Fx patients were recruited in the NYPH emergency department and started study drug (atorvastatin or matched placebo) at the time of recruitment (at least 4 h prior to surgery). THR and TKR patients were recruited at HSS at the time of pre-admission testing (typically 7–10 days prior to surgery) and started study drug 4 days prior to surgery. Study drug was continued until POD 45. Patients were called on POD 7, 14, 21, 28, 45, 90 to screen for adverse events. Patients were given an addressed, stamped envelope in which to return their pill bottle and any remaining capsules on POD 45. Because atorvastatin is an FDA-approved medication with an excellent safety profile, there were no interim analyses or stopping guidelines. The study was approved by the Institutional Review Boards at NYPH and HSS, registered with clinicaltrials.gov (NCT02197065), and performed from September 2014 to July 2016 (the end of the funding period). All participants provided written informed consent in accordance with the Declaration of Helsinki.

Serum samples for hs-cTnI and hs-CRP testing were collected at baseline and on POD 2 from all patients and stored in cryogenic tubes at -70°C [51]. THR and TKR patients also had plasma samples drawn for IL-6 testing at baseline and POD 2 which were immediately placed on ice,

double spun in the cold within 30 min, and stored in cryogenic tubes at -70°C . Upon completion of the trial, testing for hs-cTnI and hs-CRP was performed on batched samples at Washington University in St. Louis, and testing for cytokines was performed at the University of Utah. All laboratory testing was performed by study personnel blinded to patient treatment assignment and outcomes.

High-sensitivity cardiac troponin I was measured using a chemiluminescent microparticle immunoassay on an Abbott Architect i2000SR analyzer. This fifth generation high-sensitivity assay is not yet FDA-approved, and results were not used for clinical care. The lower limit of detection is 1.1 pg/mL, and the 10% coefficient of variation is 4 pg/mL. The 99th percentile of normal is 26 pg/mL (99th percentile for females = 16 pg/mL, for males = 34 pg/mL). Based on the individual and analytic variability of the test, we defined a rise in hs-cTnI as a change from baseline to POD 2 of ≥ 10 pg/mL [2]. Hs-cTnI measurement has less analytic variability than standard troponin testing which allows more precise reporting of changes in troponin above the 99th percentile, and confidence that a significant change in hs-cTnI represents myocardial injury rather than analytic variability of the test [39].

High-sensitivity C-reactive protein: Roche Diagnostics High Sensitive Cardiac C-Reactive Protein (Latex) was measured using a particle enhanced immune-turbidimetric assay. The coefficient of variation at 1.2 mg/L = 7.7% and at 11.5 mg/L = 2.2% (source: package insert; confirmed by in-house method evaluation).

Cytokine testing was performed using the Luminex Multi-Analyte Profiling system, an instrument that uses a standard sandwich capture format [12, 28, 29]. The flow cytometry technology utilizes polystyrene microspheres labeled with 2 fluorescent fluorophores. Two lasers interrogate the microsphere, with 1 used for identification of the bead according to the ratio of the 2 internal fluorophores, while the other

laser quantifies the amount of analyte bound to the microsphere. As we were utilizing the Luminex platform for IL-6 measurements, we simultaneously captured data on a panel of other cytokines (e.g., IL-1 β , IL-2, IL-2r, IL-4, IL-5, IL-8, IL-10, IL-12, IL-13, IL-17, TNF- α , IFN γ , and sCD-40L).

Statistical Analysis We used a modified intention-to-treat analysis in which patients who received at least 1 dose of study drug (or placebo) postoperatively were included. We calculated that with 30 participants, we would have > 95% power to detect a rise in hs-cTnI in > 50% of patients. With a sample size of 30 (15 for each group), we would have 70% power to detect a 30% difference in the rise in hs-CRP levels in atorvastatin- vs. placebo-treated patients. Continuous variables were tested for normality using the Shapiro-Wilk test. Normally distributed variables were summarized as mean $\pm$ standard deviation and compared using an ANOVA test. Non-normally distributed variables were summarized as median [25th percentile, 75th percentile] and compared using the Kruskal-Wallis test. Categorical variables were summarized as frequency (proportion) and compared using Fisher's exact test. POD 2 cytokine levels were modeled as a function of baseline levels and randomization to atorvastatin using generalized linear models. Non-normally distributed cytokine levels were transformed appropriately prior to analysis. We used Spearman's rho (ρ) to quantify correlation.

Results

Five hundred fifty-six patients were screened, and 22 patients were recruited (Fig. 1). Two patients withdrew after consent: 1 developed preoperative atrial fibrillation and was started on a statin, and the other refused the study drug.

Fig. 1. Recruitment flow diagram.

Table 1 Baseline patient characteristics

	Atorvastatin (<i>n</i> = 10)	Placebo (<i>n</i> = 10)
Age at time of surgery, median [IQR]	71 [67, 76]	75 [72, 84]
Elective arthroplasty	8	8
Female, <i>n</i>	8	6
BMI, median [IQR]	23.8 [22.7, 32.0]	23.5 [21.0, 27.3]
White, <i>n</i>	9	9
Non-Hispanic, <i>n</i>	10	10
Hypertension, <i>n</i>	2	1
Smoking status		
Past (> 1 year ago), <i>n</i>	5	5
Never, <i>n</i> (%)	5	5
COPD, <i>n</i>	0	1
Prior VTE, <i>n</i>	1	2
Hospital stay, days, median [IQR]	3 [3, 5]	4 [3, 5]
Duration of study drug, days, median [IQR]	49 [46, 49]	49 [36, 49]
Stopped study drug prematurely, <i>n</i>	1	3

BMI body mass index, COPD chronic obstructive pulmonary disease, VTE venous thromboembolism, IQR interquartile range

Most participants were elderly, female, and Caucasian (Table 1). Hip Fx patients were significantly older than THR and TKR patients ($p = 0.006$), had longer hospitalizations ($p < 0.001$), and were more likely to have had venous thromboembolism (VTE) in the past ($p = 0.053$). There were no significant differences in baseline characteristics, length of stay, or duration of study drug between atorvastatin and placebo-treated patients ($p > 0.10$ for all comparisons).

Perioperative medications are shown in Table 2. There were no significant differences ($p > 0.10$ for all comparisons) in medications prescribed to atorvastatin- vs. placebo-treated patients in the hospital, but prior to admission, more atorvastatin-treated patients took NSAIDs than placebo-

Table 2 Medications prescribed during hospitalization

	Atorvastatin (<i>n</i> = 10)	Placebo (<i>n</i> = 10)
Preoperative medications		
Aspirin	5	7
Beta blocker	1	1
Steroids	1	1
NSAID	6	4
Intraoperative medications		
TXA	7	6
Dexamethasone	7	7
Hydrocortisone	1	0
VTE prophylaxis		
Heparin	1	1
LMWH	2	0
Warfarin	2	1
Aspirin	7	8
IPC	5	4

NSAID nonsteroidal anti-inflammatory drug, TXA tranexamic acid, LMWH low-molecular-weight heparin, IPC intermittent pneumatic compression, VTE venous thromboembolism

treated patients (50 vs. 0%, $p = 0.033$). The majority of patients received some form of intraoperative corticosteroid (either dexamethasone or hydrocortisone), and most THR and TKR patients received intraoperative tranexamic acid (TXA).

There were 21 adverse events (AE), and 6 of them were serious AE (SAE) (Appendix Table 3). AE and SAE rates did not differ between patients randomized to atorvastatin vs. placebo (all $p > 0.10$). No patient experienced MI, stroke, transient ischemic attack, atrial fibrillation, or death. One hip Fx patient randomized to atorvastatin experienced a calf DVT on POD 15 for which she was hospitalized and anticoagulated.

At baseline, 80% of the patients had detectable hs-cTnI (> 1.1 pg/mL). One hip Fx patient had hs-cTnI > 99 th percentile of normal preoperatively indicating myocardial injury. (Using the 99th percentile of normal for women, 3/4 hip Fx patients had preoperative myocardial injury.) Twenty percent of the patients had a perioperative rise in hs-cTnI (≥ 10 pg/mL), which was not blunted by atorvastatin (Fig. 2). A perioperative rise in hs-cTnI was seen in 50% of hip Fx patients and 12.5% of the THR/TKR patients ($p = 0.16$).

Ninety-five percent of patients experienced a perioperative rise in hs-CRP, which was not blunted by atorvastatin (Fig. 3). There was a modest correlation between baseline hs-cTnI and hs-CRP values ($\rho = 0.5$, $p = 0.03$), but not between POD 2 levels, or the change in level from baseline to POD 2 (both $p > 0.10$). The degree of perioperative hs-CRP rise was not affected by the use of intraoperative dexamethasone/hydrocortisone ($p = 0.61$).

There was an increase in IL-6 levels from baseline to POD 2 in 100% of THR/TKR patients ($p < 0.001$) which was not affected by atorvastatin ($p = 0.81$) (Fig. 4). There was a trend toward a significant decrease in IL-4 levels on POD 2 ($p = 0.037$), which was not affected by use of atorvastatin ($p = 0.41$). There was an increase in IL-5 at POD 2 ($p = 0.043$), which was blunted by atorvastatin ($p = 0.041$) (Appendix Fig. 5 and Appendix Table 4). There was a moderate correlation between POD 2 IL-6 and POD 2 hs-cTnI levels ($\rho = 0.59$, $p = 0.02$), but not between baseline levels or the change from baseline to POD 2 (both $p > 0.10$). The mean ($\pm$ standard deviation) increase in IL-6 level was 17.9 ± 14.2 for those receiving dexamethasone vs.

Fig. 2 High-sensitivity cardiac troponin I at baseline and on postoperative day 2.

Fig. 3 High-sensitivity C-reactive protein at baseline and on postoperative day 2.

23.2 ± 14.5 for those not ($p = 0.58$). There were no statistically significant changes in POD 2 levels of IFN γ , IL-12, IL-13, or IL-2r (all $p > 0.10$). The levels of IL-1 β , IL-2, IL-8, IL-10, IL-13, IL-17, TNF- α , and sCD-40L could not be normalized for analysis.

Discussion

Orthopedic patients are at risk for adverse postoperative CV outcomes. In this RCT of atorvastatin vs. placebo in orthopedic patients, we demonstrated postoperative myocardial injury (as measured by a rise in hs-cTnI from baseline to POD 2) in half of hip fracture patients and 12.5% of arthroplasty patients. Eighty percent of the patients had detectable hs-cTnI levels (> 1.1 pg/mL) at baseline, and 1/4 hip Fx patients had evidence of subclinical myocardial injury prior to surgery.

Every patient in our study had evidence of perioperative inflammation. Specifically, from baseline to POD 2, 95% of patients had a rise in hs-CRP and 100% had a rise in IL-6. However, atorvastatin 40 mg daily had no

effect on the change in serum hs-CRP levels from baseline to POD 2.

Recruitment challenges encountered in this trial suggest that a large statin RCT in orthopedic patients may not be feasible. Although atorvastatin was well-tolerated, recruitment was limited by comorbidities in hip Fx patients (e.g., dementia), the reluctance of elective THR and TKR patients to take an “investigational” drug, and statin use in 40% of the target population. Patients with established cardiovascular disease were excluded because of ethical concerns about assigning them to placebo. However, perioperative statin therapy is underutilized, even among high-risk patients undergoing cardiovascular and vascular surgery [49].

We did not detect an effect of atorvastatin on postoperative ischemia as measured by the change in serum hs-cTnI level from baseline to POD 2; however, this pilot trial was not powered to do so. Atorvastatin also did not blunt the postoperative rise in IL-6 levels. Finally, none of our patients experienced myocardial infarction, stroke or transient ischemic attack, atrial fibrillation, or death during the first 90 days after surgery.

It is of interest that IL-6 levels rose in all patients postoperatively even though 70% of them received intraoperative dexamethasone. We were underpowered to show a difference in IL-6 levels between dexamethasone-treated and untreated patients (17.9 ± 14.2 vs. 23.2 ± 14.5 , $p = 0.58$), but in another trial, perioperative corticosteroids were shown to abrogate the IL-6 spike after bilateral knee arthroplasty [19].

Strengths of our trial include its randomized, double blind, placebo-controlled design, and its novel target population. Limitations include the small sample size and patient heterogeneity (hip Fx vs. THR and TKR).

The high frequency of subclinical perioperative myocardial injury documented in our study is important, because even mild elevations in hs-cTnI presage higher rates of MI, stroke, and death [8, 25]. For example, Nagele et al. found that preoperative hs-TnT elevation (> 14 pg/mL) is associated with a doubling of a 3-year mortality [31]. Similarly, postoperative hs-cTnI values as low as 20 pg/mL predicted 30-day mortality in the VISION study of 15,133 patients undergoing non-cardiac surgery [48]. In hip fracture patients, 30-day mortality is > 3 times higher in patients with a perioperative rise in hs-cTnI [15]. Finally, a recent meta-analysis of 11 studies in 2193 non-cardiac surgery patients (including 5 studies in 993 orthopedic patients) demonstrated that postoperative troponin elevation doubles the odds of dying during the year after surgery [11]. Although 1 recent hip fracture study demonstrated an association between postoperative troponin elevation and mortality only in patients diagnosed with an acute coronary syndrome, clinicians in that study were not blinded to troponin measurement [47].

Our finding of elevated postoperative IL-6 levels following orthopedic surgery is consistent with other studies [4, 7, 9, 19, 34, 43, 46]. IL-6 mediates the transition from innate to adaptive immunity [18, 41]. Trauma (such as surgery) triggers innate immune responses [45], and excessive innate

Fig. 4 Interleukin-6 levels at baseline and on postoperative day 2.

immune system activation after arthroplasty is associated with a longer time to functional recovery and slower resolution of fatigue and pain [13]. Higher IL-6 level are associated with increased mortality after hip fracture surgery [46] and in other populations [16]. In our study, IL-6 and hs-cTnI levels were correlated on POD 2 ($\rho = 0.59$, $p = 0.02$).

In summary, this pilot RCT demonstrated a high prevalence of postoperative myocardial injury, as measured by hs-TnI, not only in hip Fx patients but also THR and TKR patients. Both hs-CRP and IL-6 were elevated on POD 2, and there was a moderate correlation between POD 2 IL-6 and hs-cTnI levels, but we were underpowered to demonstrate any reduction in postoperative inflammation from atorvastatin.

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Appendix

Table 3 Adverse events

	Atorvastatin ($n = 10$)	Placebo ($n = 10$)
Adverse events (AE), n	10	11
VTE	1	0
Infection	4	2
Delirium	2	2
Hypertension	2	1
Other	1	6
Patients with at least 1 AE, n	5	4
Serious adverse event (SAE), n	2	4
VTE	1	0
Infection	0	1
Delirium	0	1
Hypertension	1	0
Other	0	2
Patients with at least 1 SAE, n	1	2

VTE venous thromboembolism

Compliance with Ethical Standards

Conflict of Interest: Jaclyn D. Szymonifka, MA; Matthew T. Rondina, MD, MS; Margaret Bogardus, BA; Scott C. Woller, MD; Scott M. Stevens, MD; Kerri Merritt; Gerard Moskowitz, PhD; Alejandro Gonzalez Della Valle, MD; and Eva Flores, MD, have declared that they have no conflict of interest. Mitchell G. Scott, PhD, reports a grant from Abbott Diagnostics during the conduct of the study. He also reports grants from Instrumentation Laboratory and Siemens Healthcare; other from Becton, Dickinson and Roche Diagnostics, outside the work. Anne R. Bass, MD, reports grants from Weill Cornell Clinical and Translational Science Center (UL1TR000457-06) and other from Pfizer and Abbott Labs during the conduct of the study. Charles Eby, MD, reports grants from Siemens Healthcare Diagnostics and personal fees from Boehringer Ingelheim and Bayer Pharmaceuticals, outside the work. Brian F. Gage, MD, MSc, reports ownership of stock in at least 1 pharmaceutical company that markets or manufactures statins.

Human/Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

Informed Consent: Informed consent was obtained from all patients for being included in the study.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

Fig. 5. Cytokines levels at baseline and on postoperative day 2.

Fig. 5. (continued)

Table 4 Atorvastatin effect on perioperative cytokine levels. This data demonstrates that the preoperative levels of the cytokines predicted the postoperative levels, and that atorvastatin did not significantly affect the change in cytokine levels, with the possible exception of IL5 ($P = 0.043$). The negative intercept for IL-4 indicates a significant decline after surgery, while positive intercepts for IL-5 and especially IL-6 indicates significant rises after surgery.

	β -coefficient $\pm$ SE	p value
IFN γ		
Intercept	1.9 ± 1.3	0.15
Preoperative, square root	1.8 ± 0.4	< 0.001
Atorvastatin	-1.4 ± 1.1	0.24
IL-12, log-transformed		
Intercept	-0.5 ± 0.3	0.18
Preoperative, log-transformed	0.6 ± 0.2	0.018
Atorvastatin	0.2 ± 0.5	0.63
IL-4, log-transformed		
Intercept	-0.8 ± 0.3	0.037
Preoperative, log-transformed	0.5 ± 0.2	0.041
Atorvastatin	0.4 ± 0.4	0.41
IL5, log-transformed		
Intercept	0.4 ± 0.2	0.029
Preoperative, log-transformed	0.4 ± 0.1	0.004
Atorvastatin	-0.5 ± 0.2	0.043
IL13		
Intercept	-5.1 ± 9.8	0.61
Preoperative, log-transformed	7.6 ± 3.4	0.044
Atorvastatin	-1.5 ± 3.9	0.71
IL-6		
Intercept	20.7 ± 4.3	< 0.001
Preoperative, log-transformed	7.3 ± 2.6	0.015
Atorvastatin	1.5 ± 6.2	0.81
IL-2r		
Intercept	-12.7 ± 44.2	0.78
Preoperative	1.2 ± 0.01	< 0.001
Atorvastatin	15.9 ± 35.3	0.66

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