Applications of Thromboelastography (TEG) in Microsurgery: A Systemic Review and Meta-Analysis

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Abstract

Viscoelastic testing including thromboelastography (TEG) and rotational thromboelastometry (ROTEM) has gained increasing popularity across many medical fields in recent years. As TEG/ROTEM testing usesawhole blood sample and evaluates interactions between cellular components i.e., platelets, red blood cells and the clotting factors, these evaluations are uniquely capable of assessing coagulation in an in-vitro environment, resembling native conditionsunlike those of conventual clotting tests (CCTs). While viscoelastic based protocols and applications are more commonplace in hepatic and cardiac surgery and trauma scenarios, results have attracted the attention of additional disciplines including microsurgery. TEG/ROTEM tests, with their ability to assess forreal-time risk of excessive bleeding or thrombosis, may be useful in the monitoring of microsurgery patients who may be at an increased risk for flap failure. The following review of TEG/ROTEM testing focuses on the most common applications of these coagulation tests and the evidence that does or does not support such uses. A systematic review and meta-analysis of the current application of TEG/ROTEM in microsurgery is reported along with an emphasis on the future that it might hold for the field. **(TCM-GMJ March 2023; 8 (1):P73-P79)**

Keywords: Microsurgery; Plastic Surgery; TEG; Thromboelastography; Implications; Thrombosis; Coagulation; Viscoelastic Testing, ROTEM.

Introduction

Perioperative bleeding due to impaired hemostasis following surgical intervention is associated with increased morbidity and mortality (1). Furthermore, thromboembolic events such as deep vein thrombosis (DVT), pulmonary embolism (PE), and myocardial infarction (MI) may occur after surgery due to a generalized hypercoagulable state in combination with underlying conditions. These complications lead to increased postoperative morbidity and mortality (2). The balance between hyper and hypocoagulability is most commonly monitored by observing abnormalities in measures such as prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT), and fibrinogen levels. While these conventional coagulation tests (CCTs) are used ubiquitously, their accuracy is restricted by several important limitations. Primarily, these tests do not provide real-time monitoring (3), and indeed, they were not created with the intention to predict bleeding, clot formation or guide coagulation management in the surgical setting (4). Considering such drawbacks, many have sought alternative measures that may be used in conjunction with CCTs.

Viscoelastic tests including thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are point of care coagulation analyses, performed on whole blood samples rather than serum that deliver a global picture of hemostasis. As TEG/ROTEM evaluate interactions between cellular components i.e., platelets, red blood cells and the clotting factors in the whole blood environment, these tests are uniquely capable of assessing coagulation in-vitro, and provide information that cannot be supplied by CCTs.

Promising results have been reported with the use of TEG/ROTEM coagulation monitoring in hepatic surgery (5), cardiac surgery (6), for trauma patients (7),obstetric and neonatal monitoring(8), and transplant surgery especially in pancreas and simultaneous kidney and pancreas transplants (SPK) (9), among others. In addition to these more established uses, the field of microsurgery may also benefit from TEG/ROTEM monitoring considering the detrimental impact of clotting derangements on flap survival. However, only a few publications have addressed microsurgical applications.

In recent years, microsurgery, which involves free tissue transfer and subsequent microvascular anastomosis, has made many advances resulting in flap survival rates increasing dramatically (10). However, flap loss still remains a recognized complication leading to higher morbidity, increased costs, and longer hospital stays (11). These failures are often due to thrombosis which may be the result of a hypercoagulable state, circulatory stasis, longer surgical durations, improper techniques, or any preexisting patient related factors such as age, diabetes, autoimmune disorders, and hereditary or acquired coagulation disorders (12,13). TEG/ROTEM tests, with their ability to assess the real-time risk of excessive bleeding or thrombosis, may be useful in the monitoring of microsurgery patients who may be at an increased

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risk for flap failure.

Although there has been a considerable amount of attention directed at answering whether TEG/ROTEM testing is beneficial in various surgical sub-specialties, to the authors' knowledge, no study design has provided a comprehensive look atthebenefits of TEG/ROTEM in microsurgery. The objective of this study is to perform a review of current applications of TEG/ROTEM and a systematic review and meta-analysis to assess clinical outcomes ofTEG/ROTEM testing in microsurgery and to compare these outcomes with studies that have used conventional monitoring methods (CCTs). A secondary objective of this study is to evaluate chronological trends in TEG/ROTEM testing outcomes in microsurgery.Primary outcomes included the number and type of thrombotic events, flap loss rate, and flap salvage rate.The authors hypothesize that, in patients who undergo free flap surgery, TEG/ROTEM tests will be beneficialand offer non-inferior outcome compared with the conventional methods. The authors also hypothesize that the benefits of viscoelastic testing in microsurgery will be greater in the more recent applications.

TEG/ROTEM Principles

TEG (Haemonetics Corp., Boston, MA) was developed by Dr. Helmut Hartert in 1948 (14) and is an in-vitro test that involves a plastic pin attached to a torsion wire submerged in a small cuvette of sampled whole blood.This apparatus is heated to 37 °C and rotated through an arc of approximately 4.75 degrees, six times per minute to activate coagulation as would be experienced due to sluggish flow. The kinetic changes experienced by the torsion wire are transmitted to the analyzer and this ultimately provides the typical TEG waveform. Variables measured in this output include the reaction time (R), clot kinetics value (K), the maximum amplitude (MA), the angle measured from the tangential line between R and the TEG tracing (α), and the coagulation index (CI) (Figure-1). R is indicative of the concentration of soluble clotting factors in the plasma and thus correlated with PT. K is the time from R until the clot develops to a size of 20 mm and positively correlates with PT/PTT. MA is the maximum size and strength of the clot. The α angle is the speed at which fibrin is built and cross-linked. Both the MA and α angle correlate with circulating levels of fibrinogen and platelets. CI is a summation of all variables. These variables allow TEG and ROTEM to provide us with a more comprehensive and complex assessment of blood coagulability compared to that of CCTs. ROTEM (Instrumental Lab., Bedford, MA), varies in comparison to TEG in that the torsion wire pin is replaced by an optical detector. Where each of these viscoelastic tests is used depends primarily on geographical location with ROTEM being favored in Europe and TEG being favored in North America (9, 15-18).

TEG/ROTEM Compared to CCTs

Multiple problems exist with singularuse of CCTs in monitoring patient coagulation perioperatively or in traumatic/intensive care settings. First, these tests are restricted as they cannot offer real-time monitoring with turnaround times ranging from 45-60 minutes or even longer (19,20). These tests also fail to address the interdependence of the cellular and enzymatic components involved in coagulation. They only provide information on clot formation without measurement of clot dissolution or stability. Finally, they are largely quantitative tests and fail to offer insight into clot and factor quality (21). As mentioned previously, it is not surprising that these tests were not created with the intent to guide or predict the coagulative state of surgical patients.

Conversely, viscoelastic tests monitor whole-blood coagulation, providing a graphical assessment (Figure-1) of the kinetics of all stages of clot formation including initiation, propagation, strength, and dissolution (18). As such, TEG/ROTEM tests may detect and quantify underlying coagulopathies such as factor deficiencies, thrombocytopenia, heparin effects, hyperfibrinolysis and hypofibrinogenemia (22). They are quick (meaningful information can be obtained in approximately 10 minutes), affordable, cost beneficial and accurate assessments that are not only useful in the quantification and qualification of hyper and hypocoagulability, but also may be further applied to guide individualized treatment algorithms and thus reduce overall morbidity and healthcare costs (23).

Hepatic Surgery

Viscoelastic testing has been used for hemostatic evaluation in liver transplantation since the 1960's (24). Reported benefits include less fresh frozen plasma (FFP) and tranexamic acid administration and a decrease in blood loss. However, long-term survival, need for revision surgery, and post-operative hemorrhage have been similar among groups monitor by TEG/ROTEM versus CCTs (25,26). For patients undergoing hepatic transplantation, especial clinical benefits of viscoelastic testing may include the detection of hypercoagulability leading to hepatic artery thrombosis, fibrinolysis shut down and intracardiac thrombosis/pulmonary arterial thrombosis all of which have been noted in this population (24).Similarly, patients undergoing hepatic resection may also benefit from TEG/ROTEM assessment of coagulation (27).

Cardiac Surgery

Viscoelastic testing has a relatively established use in real-time coagulation monitoring during cardiac surgery. Meta-analyses have been performed to evaluate past studiesthat have assessed TEG/ROTEM guided transfusion management for cardiac surgery patients (8, 28-30). Multiple analyses found that the amount of blood products used in patients monitored with TEG/ROTEM compared to CCTs were reduced (8,28-30). One study found a reduction in thrombotic rates, re-exploration rates due to postoperative bleeding and acute kidney injuryin TEG/ROTEM monitored groups (8). However, most analysis did not find any statistically significant differences between viscoelastic versus CCT groups regarding in rates of mortality or length of hospital stay (8,29,30).

Trauma Patients

Approximately 30% of patients presenting with traumatic hemorrhage develop an associated trauma-induced coagulopathy (31). Therefore, the use of TEG/ROTEM rapid coagulation testing has been advocated for to individualize patient care beyond the standard 1:1:1 (RBC:FFP:Platelet) transfusion ratio. Indeed, point-of-care viscoelastic testing is recommended by the American and European trauma guidelines (32,33). In 2020, Cochrane et al. (34) reported thatsite-of-care viscoelastic assay testing in major trauma patients was associated with a reduction in blood product wastage and improvement in mortality.

Previous studies have shown higher survival rates with TEG/ROTEM testing(35). TEG metrics have also been shown to be predictive of hypercoagulability (36) and to correlate with the risk of PE and DVT in patients with extremity and blunt abdominal trauma in observational studies (37,38).

Other Application of TEG/ROTEM

Additional application of viscoelastic testing has been reported in obstetrics, neonatology, and SPK transplantation fields, amongmany others uses. ROTEM has successfully guided transfusion therapy for postpartum hemorrhage and may have the potential to detect pregnancy associated hypercoagulability (39). In studies using TEG to monitor patients with pregnancies complicated by preeclampsia and eclampsia, viscoelastic metrics were seen to successfully monitor hemostatic changes and to be an early predictor of severe disease (40). For neonatal monitoring, heparinase-modified TEG can better reflected term and preterm neonatal coagulation as CCTs were seen to report prolonged metrics in clinically stable infants when bleeding incidence was small (41).

In patients undergoing SPK transplant, viscoelastic testing has proven useful in preventing transplant loss from thrombosis by determining the necessity of heparin administration (42). In another study comparing the outcomes of TEG versus CCT directed anticoagulation in SPK transplant patients no graft loss was reported in the TEG-directed group, multiple grafts (7 pancreas and 4 kidneys) were lost due to thrombosis in the CCT-directed group. In the TEG-directed group use of blood product, transfusions and overall hospital length of stay were also reduced.

Methods

Literature Search

A systematic search of articles related to viscoelastic testing in microsurgery patients, was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (43). The authors conducted a comprehensive search of PubMed, Cochrane Central Registry of Controlled Trials, and the archives of the *Plastic and Reconstructive Surgery* journal from inception to January23, 2021. The initial database search was performed by the second author [SH] using relevant search terms and strategies. Duplicate, non-English and non-human studies were excluded. Date restriction was then applied to include only studies from and after the year 2000. Case reports, reviews, conference proceedings, cadaveric studies and letters to the editors were excluded. Retrospective and prospective case series were included for full-text assessment that looked specifically at the application of viscoelastic testing in microsurgery patients undergoing flap reconstruction. Following selection, a full-text article screening for content was performed. References of the included papers were also reviewed and those determined relevant were subsequently included.

Data Extraction

For the studies of relevance, data extraction was performed including: the year of publication, sample size, sample number of flaps, patient sex, average patient age, cause of reconstruction, location of reconstruction, patient comorbidities, type of flap used, number of bleeding events, number of thrombotic events, type of thrombotic event (arterial, venous, both), and partial and complete flap loss rate.

Statistical Analysis

Following data extraction, a meta-analysis was performed to evaluate the total number of flap reconstructions preformed in patients who were monitored with viscoelastic tests. In these patients the total number of thrombotic events and flap loss events were calculated. From this data, combined flap salvage rate was calculated as well. These analyses were compared to a study in which 1193 free flaps were evaluated by conventional methods and 38 flap thrombosis events occurred (3.1%), 14 flap loss events occurred (1.1%), and flap salvage rate was 63% (44).A secondary meta-analysis was performed, dividing the publications chronologically into two groups with an equal number of studies (three)in each group. The total number of free flap operations, thrombotic eventsand flap loss events were calculated and compared between the two chronologically divided groups. Flap salvage rate was also calculated and compared between these two groups.

Results

Following duplicate article exclusion 2,256 studies were found. Initially, studies were screened based on language, species, and date, after which 1,504 studies remained for further review. 1,498 articles were ruled out based on irrelevance or wrong study design. The 6 remaining studies were included in this systematic review and meta-analysis (Figure-2).

A total of 608 microsurgical flap surgeries were performed in the included publications. Among these surgeries, there were 68 flap thrombosis events (11%) and 26 flap loss events (4%). Flap salvage rate was 62%. Flap salvage rates were not significantly different between studies in which viscoelastic monitoring was used compared to those in which conventional methods was used (OR = 1.06, 95% CI=0.47, 2.41). When dividing the included studies into two equal groups based on publication date (older versus newer studies), the group with studies from 2012, 2013 and 2015 had a total of 251 flaps with 42 flap thrombosis events (17%) and 21 flap loss events (8%). Flap salvage rate was 50%. The group of studies from 2018, 2019, and 2020, had a total of 357 flaps with 26 flap thrombosis events (7%) and 5 flap loss events (1%). Flap salvage rate was 81%. The odds of flap salvage were significantly higher in more recently performed studies (OR = 4.2, 95% CI = 1.33, 13.23).

Discussion

The use of viscoelastic testing for comprehensive, accurate and rapid coagulation monitoring has shown patient related benefits in many surgical fields. As such, the use of TEG/ROTEM may be beneficial in microsurgical application. Through systematic review, 6 studies were included to evaluate overall trends and application of previously performed viscoelastic testing in the setting of microsurgical flap reconstruction (Table-1). Bleeding and thrombotic events including flap loss rates were analyzed (Table-2). Overall, a relatively high flap salvage rate was calculated in the included studies in which TEG/ROTEM testing was used to monitor coagulability. As predicted, TEG/ROTEM microsurgical monitoring versus conventional monitoring (44) had an almost identical rate of flap salvage showing the non-inferiority of viscoelastic tests to predict and evaluate hypercoagulability. Viscoelastic testing has the potential to guide in early detection and management of flap complications that otherwise may result in flap failure.

When comparing chronologically grouped studies, a significantly higher rate of flap salvage was seen in the three most recent studies. This could potentially be due to a greater understanding and ability to interpret viscoelastic testing metrics. This finding may also be related to the original cause of flap reconstruction. A significant amount of the older three studies involved patients with malignancy or trauma. Further comment on two of the three more recent studies cannot be given as these variables are not reported. However, the most recent study involved only trauma patients with excellent results, indicating that these trends are potentially not only related to flap anatomical location. Comorbidities were widely and evenly dispersed among all studies, indicating that these were most likely not directly related to the reported rate of thrombotic outcomes. While there is no doubt that microsurgical skills and equipment have improved over recent years, the use of viscoelastic testing, especially in the past few years, may also directly benefit microsurgical patient in short-term and long-term hemodynamic outcomes. Viscoelastic testing metrics may allow for thrombosis detection at an earlier time point and therefore allow for better complication management and ultimately higher flap salvage rates.

Parker et al. (45) used viscoelastic testing to determine the functional fibrinogen to platelets ratio (FPR) and evaluate whether this could be used to predict perioperative thrombotic events following free tissue transfer. A total of nine patients (31%) experienced a thrombotic event, with five of these patients experiencing flap thrombosis and of these, two eventually resulting in flap loss. Eight of the nine patients who had a thrombotic complication had an FPR>42 (sensitivity = 89%, specificity = 75% for predicting thrombotic events). Even with the small sample size used, this study showed that FPR, as determined by TEG, maybe useful as a preoperative predictor for thrombotic events in free flap patients. In a similar study, Kolbenschlag et al. (46) looked at the value of ROTEM testing in aiding in thrombosis monitoring in microsurgery patients. In multivariate binary logistic regression models adjusting for all other variables, for primary thrombotic events, an FPR >43 and a pathologic ROTEM value were strong independent predictors of thrombotic flap loss. These preliminary studies suggested that TEG testing can be performed perioperatively in order to be aware of the possibility of thrombosis, especially in high-risk patients (trauma patients, cancer cases, patients with underlying clotting disorders, etc.). Wikner et al. (47) reported the first prospective cohort study to look at viscoelastic testing in cranio-maxillofacial free flap surgery patients and compared these results to CCTs. While ROTEM metrics were not significantly correlated with thrombotic events, CCTs were also not found to predict adverse events such as thrombosis, bleeding or flap loss. These findings may be related to the underpowered nature of this study, and the authors advocated for larger trials to be performed to evaluate the benefits of TEG/ROTEM monitoring in microsurgery patients.

Zavlin et al. (48) recently performed a review comparing CCTs and TEG metrics in their microsurgery patients. TEG metrics were more predictive of hypocoagulability after heparin infusion and hypercoagulability post-operatively (CCTs incorrectly showed a hypocoagulable state in both instances). In thrombotic events, significant deviations in TEG metrics were noted while CCTs did not identify coagulation deviations in any of these patients. Contrary to these beneficial findings, Ekin et al. (49) recently published a report in which TEG analysis were unpredictive of flap complications and flap loss. However, the authors did acknowledge that there was no standard time in which coagulation tests were taken and thus results were difficult to interpret and compare to other studies. The most recent study related to viscoelastic testing in microsurgery was performed by Vangas et al. (13). It was found that ROTEM detected hypercoagulability was a significant risk factor for free flap thrombosis in the late surgery group, but not in an early surgery group. When looking at these newer studies, while some of the predictive benefits and value of viscoelastic monitoring may be questioned, the information that these tests provide may be helpful in supplementing conventional tests. Additionally, studies that showed less value in TEG/ROTEM testing were correctly identified as underpowered, retrospective, or inconsistent which significantly decreases their validity.

Conclusion

Viscoelastic testing including TEG and ROTEM evaluation has gained increasing popularity across many medical fields in recent years. While viscoelastic based protocols and applications are more commonplace in hepatic and cardiac surgery and trauma scenarios, results have attracted the attention of additional disciplines including that of microsurgery. Even as the field of microsurgery is well-established, flap thrombosis and ultimately failure is still a recognized complication and microsurgeons are in need of a reliable predictive metrics to identify patients at risk of such events. Through systematic review and meta-analysis of publications on viscoelastic testing in microsurgery flap salvage rates were found to be comparable to studies in which conventional monitoring was performed. More recent microsurgery viscoelastic monitoring has shown the merits of these tests as well as indicating the fact that microsurgeons are becoming more comfortable with interpreting the TEG/ROTEM metrics. Encouragement of larger studies and multicenter trials evaluating the implications of viscoelastic test in monitoring microsurgery patients should be encouraged. Standardization of the viscoelastic based anticoagulation protocols and a clear definition of high-risk candidates for microsurgery are also necessary. These advances will allow for early detection and successful management of hypercoagulability and help to further reduce flap complication and loss rates. It is likely that viscoelastic testing will fill the void of hypercoagulability monitoring in the future of microsurgery.

Figure Legends:

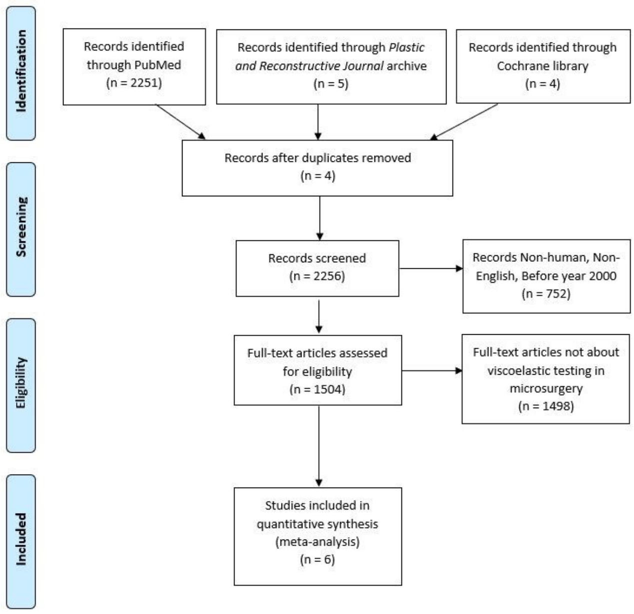

Figure-1: Thromboelastography tracing showing the variables of reaction time (R), clot kinetics value (K), alpha angle (α), and maximum amplitude (MA). R is the time from the start of the test to first fibrin formation. K is the time from R until the clot develops to a size of 20 mm. MA is the maximum size and strength of the clot. The α angle is the speed at which fibrin is built and cross-linked. This figure is currently available in "Google" and is as such a public domain entity.

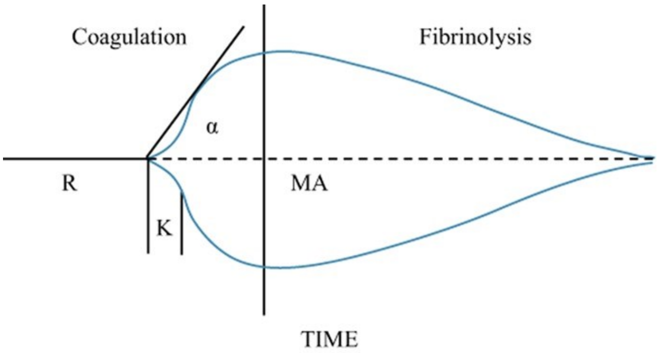

Figure-2: Search strategy for systematic review to find the currently published medical literature describing usage of the thromboelastography (TEG) in microsurgery. This figure is produced by the authors.

Publication (reference)	Year	# patients	# flaps	M¥	F¥	Age@	Malignancy	Trauma	Infection	Burns	Chronic Ulcers	Upper extremity	Trunk	Lower extremity	Head and Neck	Comorbidities	Flap type
Parker [45]	2012	29	35	17	12	58	26								29		Fibula (10), Radial (21), Other (4)
Kolbenschlag [46]	2013	181	181	108	72	50.26	45	108	12	9	7	30	39	109	3	Smoking (67), HTN# (64), Obesity (31), DM$ (14), PAD% (16)	ALT† (65), LD©(45), DIEP§ (30), Parascapular (21), Other (20)
Wikner [47]	2015	35	35	20	15	61.8	27				8	1		3	31	Smoking (18), PAD/ CAD^ (8), HTN (17), DM (5)	Fibula (15), Radial (13), Other (7)
Zavlin [48]	2018	100	172	0	100	48.2	64						100			HTN (15), DM (5), PAD (2), Smoking (23)	DIEP (98), Other (2)
Ekin [49]	2019	77	82	40	37	49.3										Smoking (28), HTN (9), DM (5), Obesity (4)	DIEP (42), Fibula (20), Radial (10), Other (10)
Vangas [13]	2020	103	103	90	13	40		103				27	2	70	4	Smoking (39), Thrombogenic comorbidities* (25)	Scap/ parascap∞ (22), ALT (14), LD © (14), Fibula (10), Other (43)

Table-1: Characteristics of Included Studies Related to Thromboelastography (TEG) Use in Microsurgery.

¥ M=male, F=female, @ = years; # = hypertension; $ = Diabetes Mellitus; % = Peripheral Artery Disease; ^ = Coronary Artery Disease; * = Includes history of previous thrombosis, ischemic disease, hypertension, obesity, neuroparesis, diabetes;† = Anterolateral Thigh Flap; § = Deep Inferior Epigastric Perforator Flap; ©=Latissimus dorsi. ∞=Scapular/parascapular

Publication (reference)	Bleeding Events	Thrombotic Events	Arterial thrombosis	Venous thrombosis	Partial flap Loss	Total Flap Loss
Parker (45)		9	3	6		4
Kolbenschlag (46)		28	6 + 7*	15 + 7*		14
Wikner (47)	7	5			1	3
Zavlin (48)	3	5	1	4		2
Ekin (49)	8	5			4	3
Vangas (13)		16				0

Table-2: Characteristics of Included Studies Related to Thrombosis and Bleeding Complications.*

in 7 cases both arterial and venous thrombosis were present.

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