To the Editor—I read with great interest the recent article by Nisanevich et al. suggesting that restricted fluid therapy for intraabdominal surgery reduces postoperative morbidity. My comments focus on the description of the statistical methods and their application to the data.

The authors mention the use of both the chi-square test and Fisher exact test for the analysis of categorical data. However, it seems that only the results for the chi-square test are reported: For the number of patients with complications, the Fisher exact test gives a nonsignificant $P$ value of 0.056. The authors should explain why they report the results of one test and not the other.

No follow-up is given for the four patients who were withdrawn after randomization because their surgeries were not considered extensive. Assuming no complications with these patients, the $P$ value would not be statistically significant by either the chi-square ($P = 0.057$) or the Fisher exact test ($P = 0.086$). The postrandomization exclusion of patients without any analysis is a serious error because the reader can never be sure why these patients were excluded.

The authors state that exact confidence intervals were calculated for the overall rate of complications, but I am unable to find these in the article. An exact 95% confidence interval for the odds ratio of an increase in complications with liberal fluid therapy is 0.95–5.14. This confidence interval includes 1 and so would not be taken to indicate a statistical difference between the two therapies.

The authors mention the use of the Newman-Keuls adjustment, but that correction only applies if the group means are independent, which is clearly not the case here.

No advanced statistical methods are used to model the data and explain the impact of relevant covariates. In particular, logistic regression could be used to model the presence of a complication on the number of fluid boluses, the degree of hypotension, the duration of surgery, or American Society of Anesthesiologists physical status. Based on these outstanding statistical issues, I agree with the authors that additional studies are needed.

Michael L. Beach, M.D., Ph.D., Dartmouth Medical School, Lebanon, New Hampshire. mlb@hitchcock.org

Reference


(In accepted for publication January 13, 2006.)

In Reply—We take this opportunity to thank Dr. Beach for his comments and showing keen interest in our recent article. Fisher exact test indeed returns exact one- and two-tailed $P$ values for a given frequency table, whereas the chi-square test of independence, which is also used in such situations, provides an approximation. However, it is an accepted practice to use the chi-square test to analyze the data in two-by-two contingency tables to test the null hypothesis when the sample size is sufficiently large and there is no imbalance in the size of the groups. Otherwise, the exact probability test devised by Fisher, Irwin, and Yates is used. Because the groups were similar in size and none of the cells had an expected frequency of less than 5, the Fisher exact test was not used to analyze the difference in outcomes between the two groups and was accordingly not provided in the article. The Fisher exact test was used to calculate the difference between the groups in other categorical data. We retrieved the files of the four patients who were excluded because surgery was not extensive to find out that one patient had a wound infection and another patient had a urinary tract infection, both of which were from the liberal group. As correctly suggested by Dr. Beach, although the number of patients with complications (which was defined as the primary end point of the study) was significantly lower in the restrictive group compared with the liberal group, no significant difference was observed in the overall rate of complications ($P = 0.21, 95\%$ confidence interval, 0.05–0.37).

Dr. Beach also commented that advanced statistical methods may have been used to model the data and explain the impact of relevant covariates. We had, in fact, considered using logistic regression. The decision to avoid complex modeling stemmed from the number of patients included in the study, which would have limited the number of covariates to be included in the model. We thought that such analyses would be more appropriate in studies including a greater number of patients.

Idit Matot, M.D.,* Sharon Einav, M.D. *Hadassah Hebrew University Medical Center, Jerusalem, Israel. idit_matot@yahoo.com

References


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To the Editor.—Cases such as that of Kent et al.1 expose the flaws and relevance of today’s widely used risk stratification systems and also show the fallacy of our and the surgical specialties’ exclusive focus on perioperative morbidity and mortality. The fact that this 97-yr-old patient’s predicted mortality was scored at only greater than 65%, despite the absolute clinical predictability of what happened, indicates that clinicians still need to use their intuition and good judgment to pick up where these scoring systems fail. More importantly, if the specialties are to consider a context of care that is applicable to all patients, from the beginning to the end of life, our interventions should be aimed at maximizing functional quality of life, not simply getting the patient through the immediate perioperative period. Therefore, as part of the preoperative evaluation and discussions with critically ill patients and their families, it must be communicated that surviving the operation is the easy part, and the postoperative period is likely to be far more trying, even highly unpleasant, for the patient and the family. As critical care physicians and anesthesiologists, we spend an inordinate amount of time discussing this frankly with family members, sometimes very graphically, in order to do whatever is necessary to get the message across.

In Reply.—We appreciate Drs. Stemp and Karras’ close reading of our case report.1 We would like to clarify that our inclusion of the acute physiology and chronic health evaluation (APACHE) II score in the case report was an attempt to provide a widely used risk stratification score for the benefit of readers of the report, rather than an explication of how we arrived at the decision to transition to palliative care. The decision to provide this patient with palliative care and how this was communicated to the patient’s family closely followed what they described as their practice, with the goal of optimizing patient comfort and functional quality of life. The APACHE II score was calculated post hoc at the time of writing the case report, and we agree with Drs. Stemp and Karras that it did not seem to correspond with our experiential-based assessment of this patient’s risk of death from this episode of illness.

Christopher D. Kent, M.D.* Brian S. Kaufman, M.D., Joseph Lowy, M.D. New York University Medical Center, New York, New York. cjmjskent@worldnet.att.net

Reference


In his 1999 Rovenstine Lecture “What We (Physicians) Can Do versus What We Should Do for the Patient,”2 Dr. Hug noted that we have eliminated the “anesthesia barrier” to operating on sick patients, but that does not mean that everybody has to have an operation before they die. We have and should act on influence and responsibilities equal to that of the surgeon in delineating risks and burdens of surgery, anesthesia, and postoperative recovery and critical illness.

Leo I. Stemp, M.D., F.A.C.C.P.,* George E. Karras, Jr., M.D., F.C.C.M. *Mercy Medical Center, Springfield, Massachusetts. leow@cox.net

References


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Leo I. Stemp, M.D., F.A.C.C.P.,* George E. Karras, Jr., M.D., F.C.C.M. *Mercy Medical Center, Springfield, Massachusetts. leow@cox.net

References


To the Editor.—We would like to report an inadvertent vaporizer selection malfunction on the North American Dräger Narkomed 2C (Dräger Medical, Danvers, MA). This incident occurred during a routine elective outpatient surgical case. Standard anesthesia machine checkout was performed as per our routine before the start of the daily workload. After intravenous induction and before placement of the endotracheal tube, the supervising anesthesiologist actuated the sevoflurane vaporizer (Tec 6 Plus; Datex-Ohmeda Inc., Madison, WI) to deliver a 3% concentration. Immediately after placement of the endotracheal tube, the supervised certified registered nurse anesthetist reached behind herself and actuated the sevoflurane vaporizer (Drägerwerk Vapor 19.1; Dräger Medical) to deliver a 3% concentration. The certified registered nurse anesthetist did this while keeping her eyes on the patient and connecting the ventilator circuit to the recently placed endotracheal tube. The attending anesthesiologist noted that both of the vaporizers were activated, and the anesthesia gas analyzer confirmed that both vapor anesthetic agents were present in the inhalation phase of respiration.

One volatile agent was selected, and the other was discontinued. The conduct of the anesthesia proceeded without event. The anesthesia machine was briefly checked for any other problems. No other malfunction was determined, and the case was allowed to proceed with the same anesthesia machine. The patient did not experience any consequence as a result of unintentional momentary dual volatile agent anesthesia. At the conclusion of the anesthesia, the anesthesia machine

Vaporizer-selection System Malfunction in the Dräger Narkomed 2C Machine

Support was provided solely from institutional and/or departmental sources.
was changed out, and the service maintenance department of North American Dräger (Dräger Technical Support, Telford, PA) was summoned to examine the machine.

The attached illustration in figure 1 demonstrates that both vaporizers were activated and delivering the set concentrations. The photograph was taken after the case was completed. The set concentrations in the photograph do not reflect the concentrations used in the case. The Dräger service engineer corrected a faulty linkage in the lever system in the back bar support for the vaporizers.

It is fortuitous that the anesthesiologists at the Ambulatory Clinical Building Operating Suite selected to have only two vaporizers mounted, desflurane (Tec 6 Plus) and sevoflurane (Drägerwerk Vapor 19.1). The desflurane vaporizer was deliberately mounted downstream of the sevoflurane vaporizer. Cross-contamination of the downstream vaporizer does not occur in this instance. The desflurane vaporizer uses vapor injection technology via an electromechanical control system to deliver the set concentration.

As a result of this design, there is no part of the fresh gas flow entering the vaporizing chamber in the desflurane vaporizer. Therefore, the vaporizing chamber is completely isolated from the fresh gas flow. Our decision to place the vaporizers in this manner resulted in preventing contamination of the downstream vaporizer in this instance.

The downstream vaporizer would certainly have been contaminated if the position of the sevoflurane and the desflurane vaporizers were reversed. A portion of the desflurane-laden fresh gas flow would enter the downstream sevoflurane-vaporizing chamber because of the design of that vaporizer. Some of this desflurane would then dissolve into the sevoflurane solution in accordance with the solubility coefficient of desflurane in liquid sevoflurane. This would adulterate the sevoflurane vaporizer for subsequent use, because both sevoflurane and desflurane would be delivered when this vaporizer is actuated. This would have resulted in further delay due to the need to wash out the contaminant in the downstream vaporizer. As it was, the anesthesia machine was back in operation the next day.

The literature has reports of anesthesia vaporizer selection malfunction. Vaporizer failure has been reported after inversion or tilting of the vaporizer when filling the reservoir.1 Vaporizer malfunction at low flow has been reported with the ADU desflurane vaporizer (Anesthesia Delivery Unit; Datex-Ohmeda, Stockholm, Sweden).2 User-removable vaporizer malposition has been reported to result in vaporizer failure.3 Understanding the technology behind new equipment and upgraded equipment is essential to understanding its limitations, as is seen in this report of the desflurane Tec6 Plus vaporizer.4

As far as we can determine, this is the first documented failure of the vaporizer-selection system in the Dräger Narkomed 2C. We publish this because this model is a common workhorse in American anesthesia practice. Our first delivery of this machine type was in September 1996. Our oldest machine is therefore 9 yr old and the youngest Narkomed 2C is 5 yr old at the time of this letter. All of our anesthesia machines are serviced and maintained as per manufacturer’s guidelines.


‘University of Texas M. D. Anderson Cancer Center, Houston, Texas. skee@mdanderson.org

References

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In Reply—Dräger Medical Inc. believes safety is paramount in anesthesia delivery. Extensive and redundant safety measures are built into all of Dräger Medical’s anesthesia delivery devices.

In response to the letter from Dr. Kee et al., Dräger Medical submits the following information. The Narkomed 2C anesthesia machine (Dräger Medical, Telford, PA) was manufactured from 1993 through 1999. This machine was manufactured with an exclusion system that, when used in conjunction with Dräger 19.1 vaporizers, Dräger 2000 vaporizers, and Datex-Ohmeda Tec 6 Plus vaporizers (Madison, WI), is designed to prevent the use of more than one anesthetic agent at a time.

The exclusion system in the Narkomed 2C incorporates a cam and lever interlock system into the vaporizer bank to prevent accidental activation of more than one vaporizer. As a result of normal use, this system may require periodic adjustment to maintain system integrity.

Therefore, Dräger Medical provides specific daily and pre-use equipment checkouts. The Narkomed 2C operator’s manual provides a recommended daily checkout for operators. The ‘Vaporizer verification’ section includes checking the vaporizer exclusion device to ensure that only one vaporizer can be turned on at a time. In addition, the Dräger-Vapor 19.1 Instructions for Use contain a ‘Checks before starting anesthesia’ section, which states that it should only be possible to operate one vaporizer at a time. Both checks indicate that if the exclusion test is not successful, the anesthesia machine should not be used until the aforesaid adjustments are made.

Robert Clark, M.B.A., M.Eng., Dräger Medical, Telford, Pennsylvania. rob.clark@draegermed.com

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Deep Vein Thrombosis after Recombinant Factor VIIa Infusion to Control Severe Recurrent Postoperative Bleeding

To the Editor—Several case reports have suggested that recombinant factor VIIa (rFVIIa, Novoseven®; NovoNordisk A/S, Copenhagen, Denmark) would be an effective therapy to control severe postoperative bleeding for patients without preexisting coagulopathic disorder.1–3 Furthermore, a recent placebo-controlled study has shown that prophylactic rFVIIa administration can reduce blood loss and erythrocyte transfusion for patients undergoing abdominal prostatectomy.4 Although the optimal dose and the usefulness of additional bolus are not established for perioperative bleeding, most reports emphasized the efficacy and the safety issue after rFVIIa administration. However, treatment-related thrombotic complications have been suggested, but in the few cases reported, the cause-and-effect relation has never been clearly demonstrated.

A 69-yr-old man with a medical history of diabetes mellitus and arterial hypertension was hospitalized for hematuria and left lower limb lymphoedema. The scanner showed two bladder tumors and a left iliofemoral venous thrombosis. Doppler-echography confirmed a complete iliac, femoral, and popliteal venous thrombosis. The endoscopic bladder resection led to the diagnostic of high-grade multifocal urothelial carcinoma. The patient was discharged from the hospital with an anti–vitamin K therapy by fluindione.

Three months later, and 25 days before a second cystoscopy, another Doppler-echography was performed and showed venous permeability with only residual parietal change on the common femoral vein. A relay of fluindione by low-molecular-weight heparin (Tinzaparin; 12,000 UI/day) was initiated 5 days before surgery. Tinzaparin was stopped the day before cystoscopy. All biologic parameters before surgery were within the normal range, and at this time, there was no clinical evidence of deep venous thrombosis resurgence. The cystoscopy led to a second endoscopic bladder tumor resection, and continuous bladder irrigation with normal saline was instituted. Immediately after surgery, persistent blood loss through the bladder catheter was noticed. The persistent bleeding diathesis led to two additional hemostatic endoscopic procedures. However, the hemorrhagic diathesis remained refractory to surgery, and the patient was admitted to the intensive care unit. Despite persistent blood loss through the bladder catheter, the mean arterial pressure and heart rate remained stable without catecholamine infusion. Moderate hypothermia (35°C) was recorded. Hemoglobin decreased to 5.7 g/dl, reaching 9.1 g/dl after a transfusion of 3 units packed erythrocytes. Despite two additional fresh frozen plasma transfusions, the hemorrhagic diathesis persisted, and the hemoglobin concentration decreased approximately of 0.5 g/dl per hour. A moderate dilutional coagulopathic disorder occurred (prothrombin time, 17 s; activated partial thromboplastin time, 39 s; and platelet count, 147,000/mm³).

Ten hours after admission, a first dose of rFVIIa at 90 μg/kg was given. At the end of the infusion, bladder irrigation fluid became clear, and hemostasis was definitively achieved. Eight hours later, an additional 70 μg/kg rFVIIa bolus was given to prevent bleeding recurrence. The following day, systematic Doppler-echography revealed a femoral deep venous thrombosis recurrence, without any clinical symptom. A therapy by unfractionated heparin was initiated, without any hematuria recurrence. The patient was discharged from the hospital 10 days later with anti–vitamin K therapy, without any new Doppler investigation.

The extended use of rFVIIa in the perioperative period opens a new way in the management of refractory bleeding and has clearly generated enthusiasm, given the abundance of case reports. There is evidence that rFVIIa is a potent prohemostatic agent that may potentially lead to thromboembolic events. Experimental and clinical studies, however, support that rFVIIa enhances hemostasis at the site of injury without systemic coagulation activation, because thrombin is generated after rFVIIa infusion where tissue factor and activated platelets are localized. This explains that most of reports regarding rFVIIa efficacy underline the tolerance, with no or little evidence of treatment-related thrombotic events.5–7 Indeed, very few thrombotic episodes are reported in the literature. However, coexisting risk factors contributing to thrombotic complications are often found, especially preexisting vessel wall damage such as atherosclerosis.8–10 In our case, we cannot exclude that the deep vein thrombosis recurrence occurred between the second Doppler-echography and surgery, but the absence of any clinical evidence and the prescription of an effective anticoagulant treatment do not support this hypothesis. In this way, it could be suggested that endothelium healing was not achieved, leading to permanent tissue factor exposition and/or platelet activation and allowing the recurrence of thrombosis after rFVIIa infusion.

The recurrence of deep venous thrombosis may also be related to the rFVIIa dosage and to an adverse side effect of the additional prophylactic bolus 8 h later. The recommended dose of rFVIIa to stop bleeding for hemophilic patients seems to be well established, but the optimum dosage of rFVIIa for patient without preexisting coagulopathy remains unclear. The lack of controlled randomized trials, the small series or single cases reported, the variability of the hemostatic abnormality leading to the bleeding diathesis, and the nature of the surgical damage do not allow us to draw any standard guidelines. As a result, available data indicate the efficacy of one or two infusions of 20–120 μg/kg rFVIIa to stop bleeding.11 Our patient received an initial 90-μg/kg rFVIIa bolus. No data in the literature suggest that a lower initial dose would have reduced the risk of thrombosis recurrence. Moreover, no data are available regarding appropriated rFVIIa strategy in the hours after the hemostasis achievement for nonhemophilic patients. The administration of an additional infusion of rFVIIa to prevent the hemorrhagic diathesis recurrence could only be supported by the short half-life of rFVIIa (approximately 2.9 h) and the lack of any available biologic parameters related to rFVIIa clinical effectiveness. In our case, rFVIIa reinjection may have played a role in the venous thrombosis recurrence. The usefulness and the safety of prophylactic rFVIIa reinjection to prevent bleeding resurgence still have to be demonstrated.

Therefore, rFVIIa is a potent hemostatic factor, but it should be used carefully to control postoperative bleeding for patients without preexisting coagulopathy. When hemorrhagic diathesis occurred in the postoperative period, a hemostatic surgical procedure should be first discussed, and the primary medical objective must be to correct the hemostatic parameters such as platelet count, anemia, dilutional coagulopathic disorders, acidosis, or hypothermia. Furthermore, before rFVIIa infusion, the benefit-risk balance should be evaluated, especially for patients with known atherosclerosis or thromboembolic disease. If bleeding remains uncontrolled, rFVIIa could be used as a last resort.

Cédric Pépion, M.D.,* Marie-Christine Becq, M.D., Laurent Jacob, M.D. †Hôpital Saint-Louis, Assistance-Publique Hôpitaux de Paris, France. cedric.pepion@lslsaphp.fr

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perioperative treatment of patients with a history of intraoperative awareness and post-traumatic stress disorder

To the Editor—It has been estimated that approximately 25,000 patients each year in the United States alone may experience undesired intraoperative awareness with explicit recall. A significant proportion of these individuals may subsequently develop post-traumatic stress disorder (PTSD), characterized by reexperiencing the trauma (e.g., nightmares or flashbacks), hyperarousal states (e.g., hypervigilance, insomnia, irritability), and avoidance of cues related to the initial trauma. Although there has been significant attention on the prevention of intraoperative awareness through the use of electroencephalographic measures of anesthetic depth, there has been little discussion of the treatment of patients with a history of awareness returning for surgical care and anesthesia. Here, we discuss the perioperative management of a patient who developed PTSD after awareness under general anesthesia during a tubal ligation and who returned for a further gynecologic procedure.

After the original surgery during which she was aware under general anesthesia, the patient was overly alert and unable to sleep in the recovery room, reporting severe leg and back pain. After discharge, she remained hypervigilant and experienced episodes of severe panic when seeing the color blue. Several days after the surgery, she recalled that she had been awake during her surgery and began having flashbacks of abdominal and pelvic pain. Her surgeon subsequently confirmed her recall of intraoperative events and discussions. She developed signs of PTSD, including increasing periods of irritability and worsening insomnia, as well as frequent nightmares, flashbacks, and intrusive thoughts related to the surgery. Signs of depression such as worsening insomnia, as well as frequent nightmares, flashbacks, and intrusive thoughts related to the surgery. Spinal anesthesia with mild anxiolysis was then planned. Psychological and physiologic reactivity to reminders occurred (especially to seeing people in the community or on television wearing blue scrubs), followed by avoidance of all such cues. She did not return to her original surgeon, declined further gynecologic care, and developed a distrust of anesthesiologists.

Years later, the patient returned to our institution for anterior and posterior colporrhaphies, suburethral sling, cystoscopy, and gynecologic examination under anesthesia. The circumstances of her past surgery were identified in the preoperative evaluation clinic, leading to the question: What is the optimal perioperative anesthetic plan for a patient with a history of awareness and PTSD? The strategy of general anesthesia would create severe anxiety in such a patient, for fear of reexperiencing the trauma of intraoperative awareness. Furthermore, careful examination of the anesthetic record from the initial surgery gave no clear indication of why the general anesthetic did not effectively suppress awareness. The use of neuraxial anesthesia was another strategy considered, but would also allow the patient to experience the cues of her past trauma such as surgeons, anesthesiologists, and other healthcare providers in scrubsuits. Furthermore, the use of ancillary sedation during regional anesthesia could potentially be subjectively experienced by the patient as insufficient anesthesia. There were also concerns of converting neuraxial to general anesthesia intraoperatively in the event of failed regional anesthesia or psychological events such as flashbacks.

The patient was interviewed in the preoperative evaluation clinic by an anesthesiologist who would not be her anesthesia provider, and three options were offered to her after a discussion: (1) not to proceed with the surgery; (2) have the surgery performed under general anesthesia with maximal efforts to prevent awareness; or (3) maintain total awareness by using a purely regional anesthetic. It was her preference that the final decision would be made on the day of the surgery after discussion with the anesthesiologist who would actually administer her anesthesia.

On the day of the surgery, the patient’s chart was reviewed by an anesthesiologist with specific interests in awareness under general anesthesia, and the patient was interviewed again in the preoperative holding area. The patient was extremely anxious and concerned about reexperiencing the trauma of intraoperative awareness and the anesthesiologist carefully discussed multiple anesthetic plans with her. Considering her extreme anxiety regarding general anesthesia, it was our suggestion and also her preference to have regional anesthesia to keep her fully awake during the surgery. She also agreed to general anesthesia if the regional anesthesia failed or if she had traumatic flashbacks or dissociation from reality. Spinal anesthesia with mild analgesia was then planned.

The goals were (1) to have the surgery performed under spinal anesthesia with a dense motor and sensory block that would last for the duration of the surgery; (2) to attenuate her anxiety but keep her alert enough to maintain an interactive relation with the anesthesiologist to prevent flashbacks; (3) to convert to general anesthesia in the event that she had distressing flashbacks or experienced pain; (4) to use a Bispectral Index monitor if general anesthesia was used, with target levels in the range of 30–40; and (5) to avoid long-acting neuromuscular blockade during induction in the event of general anesthesia.

The patient was given 2 mg intravenous midazolam in divided doses,
and spinal anesthesia was initiated by intrathecal injection of 18.75 mg hyperbaric bupivacaine and 20 μg fentanyl in the sitting position with a 25-gauge Whitacre needle. After assuming the lithotomy position, her anesthesia level was confirmed by pinprick to a T10 level bilaterally. The surgery was performed uneventfully, and the patient was kept fully awake and engaged during the entire surgical period. Conversations with the patient on diverse topics unrelated to surgery and anesthesia were initiated by the anesthesiologist and maintained throughout the procedure. The goal was to keep the patient engaged in the present moment and prevent dissociation or flashbacks related to PTSD. This is often referred to in psychotherapy as a “grounding technique.” The patient experienced no flashbacks or pain and was discharged home within 48 h, with positive feelings about the experience.

Patients returning for surgery with a history of awareness and PTSD will likely have a distrust of anesthesiologists and severe anxiety about reexperiencing the trauma of surgery. Although anesthetic plans must vary with the given procedure, we found that initiating a thoughtful preoperative discussion with the patient about such plans helped facilitate a rapport and a sense of control for the patient. With the use of neuraxial blockade, we found it beneficial to use minimal sedation to keep the patient engaged in the present moment, to avoid altered states of consciousness that could potentially allow traumatic memories to emerge, and to actively provide the patient with intraoperative “grounding.” A history of awareness and PTSD presents challenges to both the patient and the anesthesiologist when further surgery is required. Further consideration of its clinical management is warranted.

George A. Mashour, M.D., Ph.D.,†* Yandong Jiang, M.D., Ph.D., Janet Osterman, M.D. †Massachusetts General Hospital, Boston, Massachusetts. gmashour@partners.org

References


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