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Original Research Article

Proactive Therapeutical Modulation of the Postoperative Intraperitoneal Adhesions- the Efficacy of the Collagen-based Biomaterials (simple and composite)

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ABSTRACT

Introduction: **Postoperative peritoneal adhesions can cause severe complications, preventing methods being of a great importance, bioabsorbable membranes being able to prevent localized adhesion.**
Material and method: **The study was a single-center prospective, randomized controlled investigation, safety and efficacy of collagen-based sponge in the study group being compared to no anti-adhesion treatment in a parallel control-group, with blinded evaluation of primary endpoints.**
Results: **A significant reduction was observed in adhesion severity when the collagen sponge was applied in the laparotomy groups. Collagen sponge serves as a temporary barrier, separating apposing peritoneal surfaces throughout the healing process, being fully biodegraded and resorbed over approximately 3 to 5 weeks.**
Discussion and conclusions: **The collagen material showed good handling and was able to conform readily to the tissue contours. At the time of reintervention, in the selected cases, examination of the peritoneal cavity showed fewer adhesions, better healing of the injured surface and little or no fibrotic reaction in the cases receiving collagen-based sponge as an adhesive barrier.**

Key words: collagen sponge, peritoneal adhesion, prevention

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INTRODUCTION

The use of polymeric materials for the administration of pharmaceuticals and as biomedical devices has increased over the past decades. Biodegradable polymers have been used as drug carriers and in the form of implants or devices for fracture repair, ligament reconstruction, dental repairs, artificial heart valves, contact lenses, cardiac pacemakers, vascular grafts, tissue regeneration and surgical dressings.

Knowledge of the structure, biochemistry and biology of collagen demonstrated the importance of the collagen use in the medical practice. The first studies on collagen were undertaken by the leather and glue industries, contributing to the understanding of the cross-linking process and its correlation with the tensile strength, revealing the mechanical properties of this fibrillar protein.

Progress in several surgical specialties has been achieved through the development of new (non) biodegradable prosthetic materials, of the polymers studied, collagen having considerable and potential use in the development of surgical prostheses.

Postoperative peritoneal adhesions can cause severe complications, preventing methods being of a great importance. Numerous adhesion prevention materials have been developed, their general use being limited by the vital biological requirements, like nonadherence, biocompatibility, biodegradability in accordance with the wound healing rate, and nontoxicity.

A broad range of potential medical products based on collagen have been produced, different types being recently available commercially. Such products have generally proved to be successful, especially in the prevention of the postoperative adhesion syndrome, and include injectable collagen, haemostatic powder or fleece and replacement components for the peritoneal tissue or for the cardiovascular system, such as bioprosthetic heart valves.

The current clinical interest is focused on the use of bioabsorbable membranes, which allow localized adhesion prevention.

The purpose of this study was to investigate if collagen-based biomaterials, simple or composite, especially collagen sponges, can be an effective barrier method in preventing localized peritoneal postoperative adhesions.

MATERIAL AND METHOD

The study was a single-center prospective, randomized controlled investigation. Safety and efficacy of collagen-based sponge in the study group are compared to no anti-adhesion treatment in a parallel control-group, with blinded evaluation of primary endpoints. Primary endpoints are the evaluation of the therapeutic role of collagen sponge in reducing peritoneal adhesion formation and the need of laparotomies for adhesiolysis, with evaluation of the incidence, extent, and severity and chronic abdominal pain. 20 patients with surgical indication to laparotomy (trauma or surgical emergencies), admitted at the General Surgery Department of the "Sfântul Pantelimon" Emergency Clinical Hospital, an academic hospital of the University of Medicine and Pharmacy "Carol Davila" in Bucharest, Romania, were enrolled and randomized into two groups, from January 1st 2015 to December 31st 2015, including a 6 months follow-up interval. The first group (10 patients) received traditional treatment (control group), whereas the second group was treated with the addition of collagen sponge before the abdominal closure.

Patients were treated, as well as written informed consents for each procedure adopted were collected, according to the usual clinical practice. The study protocol conforms to the ethical guidelines of the "World Medical Association (WMA) Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects" adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013. Approval by the institutional review committee was obtained, since this study prospectively analyzed patients' data.

Inclusion criteria were: age over 18 years and under 75 years old, the high risk for peritoneal adhesion formation (patients that needed open surgical intervention, like trauma or emergencies), no peritoneal faecal contamination or sepsis and no prior open surgical intervention. Exclusion criteria were: patients under 18 years or over 75 years old, requiring of a simultaneous intervention, pregnancy or participation in other clinical investigations.

Data were recorded regarding demographics, diagnosis, duration of hospital stay, complications and mortality. The analysis of the data was made using EpiInfo, a free software created by Centers for Disease Control and Prevention, Atlanta, USA and the Microsoft Office Excel 2013 software. Probabilities less than 0.05 were accepted as significant. The data were summarised first as differences in prevalence of exposure, and then as the odds ratio.

RESULTS

Controls were recruited to match each case, e.g. if a woman of 53 years was recruited as a case, a control of similar age was selected within a range of ± 5 years.

The distribution of urban/rural and male/female variables was similar within the two groups (5 cases to 5 controls).

Regarding the surgical indication for laparotomy, 2 hemodynamically unstable trauma patients from the control group and 3 from the case group, with positive focused assessment with ultrasonography in trauma (FAST exam) or diagnostic peritoneal aspiration/lavage (DPA/DPL), underwent emergent abdominal surgical exploration in order to control life-threatening hemorrhage. The other indications for laparotomy were: 4 patients with mechanical small bowel obstruction (SBO) and 3 with large bowel obstruction (LBO) from the case group, 6 SBO subjects and 2 LBO subjects from the control group (Figure 1.The trauma / SBO /LBO cases that needed surgical intervention).

The average duration of the surgical intervention was 2h 45 min in the case group, versus 2h 30 min in the control group, with a mean interval of 10 min required for the intraperitoneal placement of the collagen-based sponge before the abdominal closure.

The immediate postoperative complications taken into consideration in the present study were: ileus, SBO, fever, intraabdominal hematoma or abscess, seroma at the surgical wound and sepsis. In the case group 4 patients suffered prolonged ileus, 6 patients had fever for over 48 h, 1 with intraabdominal hematoma and 4 with seroma. In the control group the results were similar to the case group, with slightly reduced number of patient with ileus or fever (2 patients with prolonged ileus and 4 with fever for over 48 h), 1 intraabdominal hematoma and 5 patients with seroma. No cases of SBO, abscess or sepsis were recorded in both case and control groups (Figure 2. Case-control comparison of the immediate postoperative complications)

The length of the hospital stay was an average of 13 days for the case group and 15 days for those from the control group.

Late complications of the postoperative peritoneal adhesion syndrome are known to be infertility in women, chronic abdominal pain and intestinal obstruction. Among the patients from the case group, 3 suffered chronic abdominal pain, for 1 patient surgical reintervention being indicated for SBO. 5 patients from the control group presented chronic abdominal pain within the follow-up interval and 2 patients had SBO, for whom surgical reintervention was indicated. No fertility issues in women were observed, a possible reason being the 6 months interval of follow-up. (Figure 3. Late postoperative complications in the case and control groups).

Thus, surgical re-intervention was indicated for 3 patients out of the total of 20 included in the present research, one from the case group and 2 from the control group. At the time of the re-intervention, aspects regarding severity, distribution and histopathology of the peritoneal adhesions were analyzed based on the score proposed by Coccolini et al. in 2013 (Figure 4. Peritoneal adhesion index), the results being as follows: all 3 cases presented strong, vascularized adhesions, localized bowel-to-bowel, in the central area of the abdominal cavity [1].

A significant reduction was observed in adhesion severity when the collagen sponge was applied in the laparotomy groups. Regarding microscopic study, collagen-based sponge application significantly reduced the inflammation score. Fibrosis, unlike inflammation, differs between both approaches. In the case group, fibrosis was reduced with application of the sponge, whereas in the control group greater fibrosis was observed (Figure 5. Bioabsorbable collagen sponges with gentian blue).

DISCUSSION

Postoperative peritoneal adhesion syndrome is an important cause of hospital admission, with significant morbidity and mortality, therefore representing a substantial burden for healthcare systems worldwide. No method has distinguished itself as the optimal means of preventing adhesion formation, current preventive approaches ranging from the use of physical barriers to the administration of pharmacological agents, recombinant proteins and antibodies, and gene therapy, without satisfactory results. Extensive literature on the subject demonstrates both the complexity of the issue and the myriad resources allocated to this condition, yet few interdisciplinary studies have been conducted involving experts from different fields [2].

The increasing application of alloplastic material in medicine and, particularly, in surgery creates two major problems: the need of sufficient evidence of the harmlessness of the material used, in a broad biological sense, covering all aspect of tissue-graft interactions, and the promotion of new products only when the practical advantages are demonstrated.

Two general concepts regarding the design of the biological material are known to be essential. One, the prosthesis should resemble the substituted tissue in form, structure, physical properties and functional requirements, with minimal tissue reaction. A second concept is that the tissue has the potential to form its own substitute, providing a temporary framework for ingrowth of cells and capillaries, achieving restoration in shape and size of

the original tissue, before reaching the functional transformation. These alloplastic materials must have high porosity and adequate hydrophility to allow cell ingrowth and diffusion of nutrients. Thus, the optimal prosthetic device represents an ideal, collagen-based biomaterials, due to their properties, representing a possible option as a tissue substitute.

Collagen, in various forms, has become a successful and widely spread medical material, gaining clinical and consumer acceptance, being seen as a safe biomaterial with multiple clinical applications [3]. Commercial products are available for use in a variety of medical disciplines, such as cardiology, with bioprosthetic heart valves, arterial replacements, and arteriovenous access shunts [4, 5]. In surgery, collagen based sutures, haemostats and wound dressings are available.

Collagen based membrane was demonstrated to be effective as an adhesion barrier [6].

Collagen sponge can be used for the prevention of postoperative adhesions in digestive, colorectal, gynecological, and urological surgery, in patients undergoing abdominopelvic laparotomy or laparoscopy. It serves as a temporary barrier, separating apposing peritoneal surfaces throughout the healing process, being fully biodegraded and resorbed over approximately 3 to 5 weeks.

Collagen implants, simple or composite, are enzymatically degraded into constituent amino acids, reutilized for protein synthesis or excreted as urea. The benefits of collagen use include its role in stimulating hemostasis and wound healing, as proven by Bailey et al. in 2000. The incidence of postoperative adhesions can be reduced by the intraperitoneal administration of a type 1 collagen solution before wound closure [7-9].

The collagen-based sponge must be treated for removal of viruses and prions as a further precaution. Adverse events to acellular collagen implants have been proven to be extremely rare, having low antigenicity and immunogenicity, which is further minimized by cleavage of telopeptides during the purification process [10]. Bio-resorption time has been optimized for anti-adhesion performance while minimizing the risk of infection.

Díaz-Güemes, Idoia et al., in their study "Hemostatic sponge effect on adhesion prevention in a porcine model", published in 2014, aimed to assess the preventive effect of an absorbable hemostatic collagen sponge (HCS) on the reduction of postoperative gynecological adhesions in a porcine model.Thus, the study demonstrated that HCS is a safe preventive method for gynecological use and, even though the number and extent of adhesions did not decrease with HCS, inflammation and adhesions' severity were reduced in the laparoscopic and laparotomy approaches, respectively [11].

In our study, the immediate postoperative complications that occurred were prolonged ileus, fever, intraabdominal hematoma and seroma at the surgical wound, with slightly higher incidence within the case group (4 cases of prolonged ileus, 6 patients with fever for over 48 h, versus 2 patients with prolonged ileus, 4 with fever from the control group), results that can be easily correlated with the ones showed by the recent research, that suggests that the use of adhesion barriers is associated with increased incidence of fever and ileus after myomectomy and hysterectomy, and with small bowel obstruction after hysterectomy [12]. No cases of SBO, abscess or sepsis were recorded in both case and control groups.

Togas Tulandi, MD, MHCM, from McGill University Health Center, Montreal, Quebec, Canada, and colleagues reported the results of a retrospective cohort study evaluating the data of 473,788 women, who had had uterine myoma and underwent hysterectomy or myomectomy. The data was collected from the Healthcare Cost and Utilization Project Nationwide Inpatient Sample database of 2003–2011, ileus and small intestinal obstruction being the primary outcomes, and fever, pain, abscess, intraabdominal hematoma or seroma, sepsis, secondary outcomes.

Of 473,788 women, 62,563 underwent myomectomy and 411,225 had had hysterectomy. Adhesion barrier was used in 3392 (5.4%) patients with myomectomy and in 5590 (1.4%) patients with hysterectomy. In cases in which adhesion barrier was not used, the researchers found a lower rate of ileus after myomectomy compared with the cases where adhesion barrier was used (1290/59,171 [2.2%] vs 109/3392 [3.2%]; adjusted odds ratio [OR], 1.50; 95% confidence interval [CI], 1.22 - 1.83). The researchers noted similar findings for hysterectomy cases (10,329/405,635 [2.5%] vs 288/5590 [5.1%]; adjusted OR, 1.97; 95% CI, 1.75 - 2.23).

A higher incidence of fever in the adhesion barrier group compared with the nonbarrier group after myomectomy (4.4% vs 2.9%; adjusted OR, 1.44; 95% CI, 1.21 - 1.71) and hysterectomy (2.5% vs 1.6%; OR, 1.65; 95% CI, 1.40 - 1.96) was also noted. However, small bowel obstruction registered a lower incidence in the non-barrier group compared with the barrier group in cases of hysterectomy (804/405,635 [0.2%] vs 23/5590 [0.4%]; OR, 1.90; 95% CI, 1.25 - 2.89), but not in cases of myomectomy. No SBO or LBO, as immediate postoperative complications, were observed within our study population [12].

The retrospective nature of Tulandi's study, with no detailed information about the surgery or the

type of adhesion barrier, the criteria for diagnosing ileus or small intestinal obstruction and the possibility of inaccuracy resulting from the use of an administrative database limit the statistical significance of the research. However, the strength of the study was the large number of patients involved. The authors also note that whereas the use of adhesion barrier was associated with complications, the overall incidence of complication remained low. However, the use of adhesion barrier led to a longer hospital stay, in contradiction with the result of our research that showed a shorter hospital stay for those patients included in the case group (13 days vs 15 days) [12].

In most cases of abdominal surgery, postoperative adhesion occurs and may lead to abdominal pain, intestinal obstruction, infertility, and other complications. The present study showed a low rate of postoperative adhesion syndrome complications, with 3 patients suffering chronic abdominal pain and 1 patient undergoing surgical re-intervention for SBO, in case group, 5 patients from the control group presenting chronic abdominal pain within the follow-up interval, and 2 patients having SBO, for whom surgical re-intervention was indicated. No fertility issues in women were observed, a possible reason being the 6 months interval of follow-up.

Intraoperative aspects regarding severity, distribution and histopathology of the peritoneal adhesions were analyzed at the time of re-intervention, based on the score proposed by Coccolini et al. in 2013. A significant reduction was observed in adhesion severity when the collagen sponge was applied in the laparotomy groups. Regarding microscopic study, collagen-based sponge application significantly reduced the inflammation score. Fibrosis, unlike inflammation, differs between both approaches. In the case group, fibrosis was reduced with application of the sponge, whereas in the control group greater fibrosis was observed.

CONCLUSIONS

- The collagen material showed good handling and was able to conform readily to the tissue contours.
- At the time of re-intervention, in the selected cases, examination of the peritoneal cavity showed fewer adhesions, better healing of the injured surface and little or no fibrotic reaction in the cases receiving collagen-based sponge as an adhesive barrier.
- A quantitative assessment that scored the extent, tenacity and nature of the adhesions, showed that the collagen barrier significantly reduced adhesions compared with that observed in a similar number of control patient where no barrier was employed. Histological examination confirmed that there was minimal tissue reaction.
- The use of collagen sponge as an adhesion barrier is associated with increased incidence of fever and ileus.
- Research in many laboratories has clearly demonstrated that collagen can be used in a wide range of different medical devices.
- There are many opportunities in the future for further commercial products, particularly in the emerging field of tissue engineering where collagen is a logical choice as the scaffold structures that are necessary for tissue regeneration.

Figure 1. The trauma/ SBO/LBO cases that needed surgical intervention

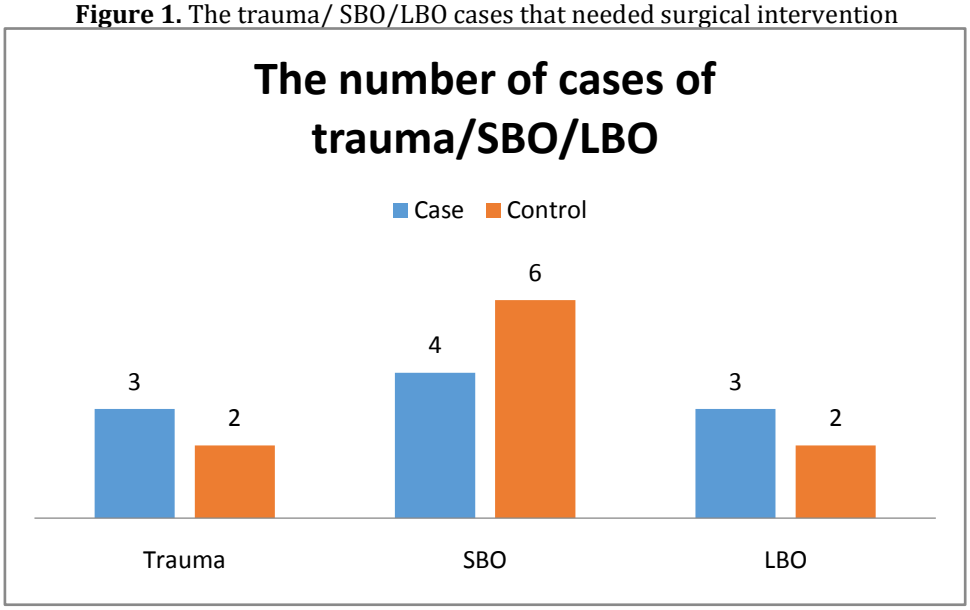

Figure 2. Case-control comparison of the immediate postoperative complications.

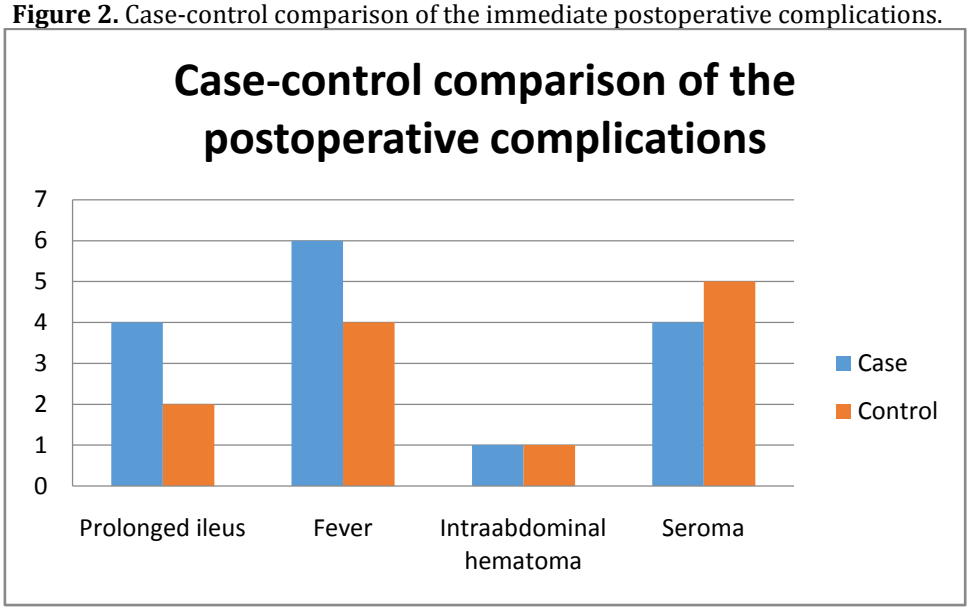

Figure 3. Late postoperative complications in the case and control groups.

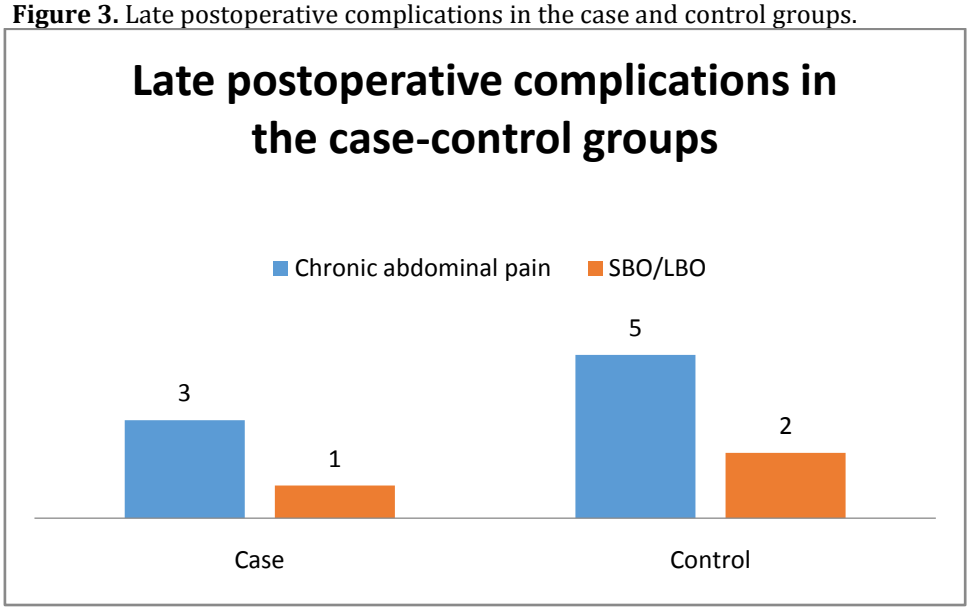

Figure 4. Peritoneal adhesion index.

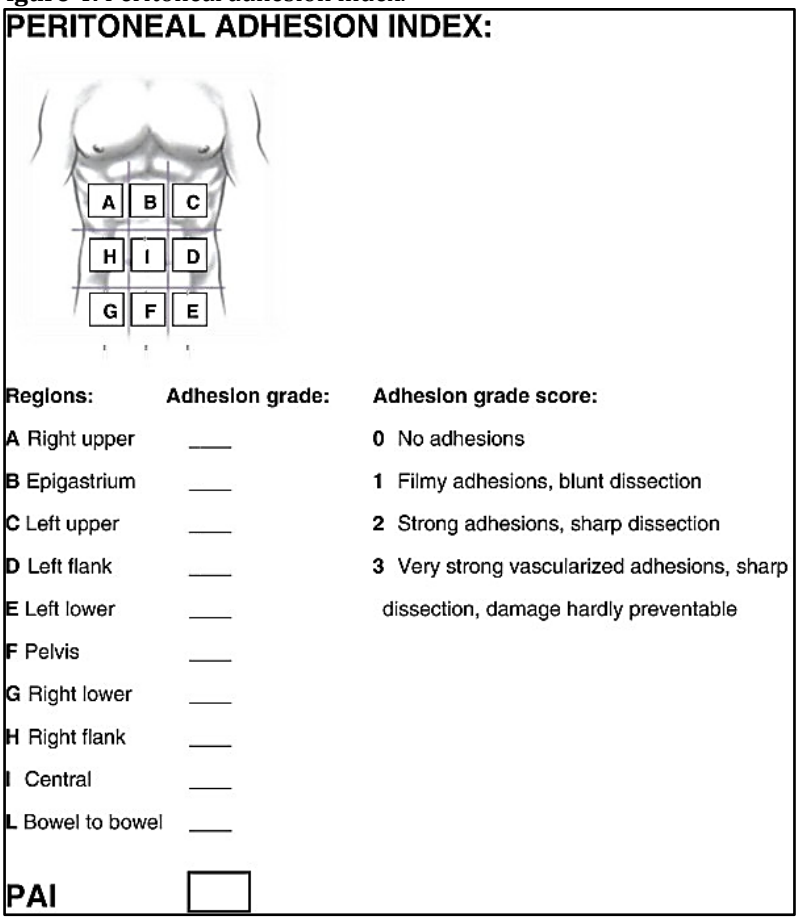

Figure 5. Bioabsorbable collagen sponges with gentian violet.

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