POSTOPERATIVE PERITONEAL ADHESIONS PROPHYLAXY USING COLLAGEN-BASED BIOMATERIALS

SIMONA BOBIC^{1,2}, VLAD DENIS CONSTANTIN^{1,2}, MĂDĂLINA ALBU KAYA⁵, ȘTEFANIA MARIN^{3,5}, ELENA DĂNILĂ^{4,5}, MIHAI DIMITRIU^{1,2}, BOGDAN SOCEA^{1,2}

¹"Carol Davila" University of Medicine and Pharmacy, Surgery Department, Bucharest, Romania

²"Sfântul Pantelimon" Emergency Clinical Hospital, Surgery Department, Bucharest, Romania

³Center of Surface Science and Nanotechnology, University Politehnica of Bucharest, Splaiul Independentei 313, Romania

⁴University Politehnica of Bucharest, Faculty of Applied Chemistry and Materials Science, Bucharest, 1-7 Gheorghe POLIZU Str., 011061, Bucharest, Romania

⁵INCDTP - Division: Leather and Footwear Research Institute, Bucharest 031215, Romania, madalina.albu@icpi.ro

Corresponding author: Vlad Denis Constantin M.D. Ph.D., Professor of Surgery „Carol Davila” University of Medicine and Pharmacy Bucharest „Sfântul Pantelimon” Emergency Clinical Hospital Bucharest 340–342 Pantelimon Street, Bucharest, Romania e-mail: constantindenis@yahoo.com

Peritoneal adhesion occurs after abdominal, gynecological, and thoracic surgeries, determining important postsurgical complications such as infertility, chronic pelvic pain and intestinal obstruction, with difficulties of extensive adhesiolysis in future surgery. Antiadhesive barrier methods, providing physical separation between the injured site and the adjacent tissues, have been developed. Taking into account the fact that physical separation is only required during the critical time of wound healing of the damaged area, bioabsorbable polymers, available in the forms of solutions, gels, and sheets, have proved to be efficient. The study presents the characteristics and limitations of the currently available antiadhesive biomaterials, mentioning the recent investigations regarding the use of collagen-based biomaterial, that show promising performance, such as ease of handling and more effective reduction of adhesion.

Keywords: peritoneal adhesions, prevention, biomaterial, collagen

INTRODUCTION

Postoperative adhesion has been reported to be responsible for 60–70% of cases of small bowel obstruction (SBO) and 15–40% of infertilities, approximately 300000 hospital readmissions annually being related to the formation of postoperative adhesions in the USA, the annual financial expenditure for pertinent treatment exceeding \$1.3 billion (Suzuki, 2012).

Strategies of prevention of adhesions can be grouped into four categories: general principles, surgical techniques, chemical agents and mechanical barriers. Antiadhesive materials are used as a physical barrier between an injured site and the adjacent tissues. Although several nonabsorbable synthetic materials such as silicone and PTFE have been shown to be effective, bioabsorbable materials are preferred because of the lack of necessity of a second surgical intervention for the removal of the nonabsorbable material. The purpose of the present study is to determine the efficiency of collagen-based biomaterials in preventing localized peritoneal postoperative adhesions, associating a review of literature related to the recent biomaterials used as antiadhesive methods.

MATERIAL AND METHOD

The study represents a single-center prospective, case-control, randomized controlled investigation of the safety and efficacy of collagen-based sponge in preventing the postoperative peritoneal adhesions.

The study group, who underwent an intra-abdominal surgical intervention followed up by intra-peritoneal application of collagen sponge, is compared to a control-group, with blinded evaluation of the therapeutic role of collagen sponge in reducing peritoneal adhesion formation and the need of laparotomy or laparoscopy for adhesiolysis, measuring the incidence, extent, severity and chronic abdominal pain.

30 patients with surgical indication to laparotomy (trauma, oncological 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 organized into two groups, from January 1st 2015 to September 1st 2017, including a 8 months follow-up interval. 15 patients receiving traditional treatment were included in the control group, those from the study group having been received intraperitoneal application of collagen sponge before the abdominal closure.

The collagen-sponge samples were made of 50x50x3 mm, made of 2mg collagen fibers derived from equine tendon covered with 4, 3-6,7mg human fibrinogen, 1, 5-2,5 IU bovine thrombine, 0,055-0,087 Ph.Eur. bovine aprotinine and 7-26mcg riboflavine. The samples were applied in the peritoneal cavity, under sterile conditions, after lavage and cleaning of the surgical site, covering the peritoneal defect, 2-3 cm beyond the edges, before the abdominal closure.

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, oncologic surgery 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.

Patients were treated, as well as written informed consents for each procedure adopted were collected, according to the usual clinical practice and to the ethical guidelines. Approval by the institutional review committee was obtained, since this study prospectively analyzed patients' data, regarding demographics, diagnosis, duration of hospital stays, complications and mortality. The analysis of the data was made using Microsoft Office Excel 2013 software.

RESULTS

Controls were recruited to match each case, with similar distribution of urban/rural and male/female variables. Regarding the surgical indication for laparotomy, 4 hemodynamically unstable trauma patients from the control group and 5 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: 6 patients with mechanical small bowel obstruction (SBO) and 5 with large bowel obstruction (LBO) from the case group, 4 SBO subjects and 6 LBO subjects from the control group (Figure 1. The trauma / SBO /LBO cases that needed surgical intervention).

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 (figure 2).

Figure 2. The average duration of the surgical intervention

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 patients with ileus or fever (2 patients with prolonged ileus and 4 with fever for over 48 h), 3 intraabdominal hematoma and 6 patients with seroma. No cases of SBO, abscess or sepsis were recorded in both case and control groups (Figure 3).

Figure 3. Case-control comparison of the immediate postoperative complications

The length of the hospital stay was an average of 12 days for the case group and 15 days for those from the control group. Evaluation of post-surgical adhesion by second-look laparoscopy was performed at 7 months after initial surgery. At the time of the evaluating laparoscopy, aspects regarding severity, distribution and histopathology of the peritoneal adhesions were analyzed based on the scores proposed by Coccolini *et al.*, in 2013, Mazuji and Zhülke, 1965.

According to Coccolini and Mazuji scores, from the case group, 4 patients presented grade 1-3 peritoneal adhesions located, predominately, in the supramesocolic compartment, with no cases of grade 4 peritoneal adhesions. From the control group, 9 patients had grade 1-3 peritoneal adhesions located diffusely and 4 patients presented

grade 4 adhesions. 11 patients from the case group and 2 patients from the control group presented no peritoneal adhesions after 7 months (figure 4).

Figure 4. Type of peritoneal adhesion according to Coccolini and Mazuji scores, at the time of the evaluating laparoscopy

According to the histopathological analysis, 3 patients presented loose or firmer connective tissue, grade 1-3 according to Zuhlke scoring, and 1 with grade 4 adhesions, from the case-group, and 10 patients from the control group had grade 1-3, with 2 cases of grade 4 (figure 5).

Figure 5. The histopathological analysis of the adhesions, according to Zuhlke classification, after 7 months

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 8 months interval of follow-up. (Figure 6. Late postoperative complications in the case and control groups).

Figure 6. Late postoperative complications in the case and control groups

Thus, surgical re-intervention was indicated for 3 patients out of the total of 30 included in the present research, one from the case group and 2 from the control group. A significant reduction was observed in adhesion incidence and severity when the

collagen sponge was applied in the case groups, reducing the inflammation and the fibrosis processes.

DISCUSSION

The present study aimed to investigate the potential of a spongy sheet composed of 2mg collagen fibers derived from equine tendon covered with 4, 3-6,7mg human fibrinogen, 1, 5-2,5 IU bovine thrombin, 0,055-0,087 Ph.Eur. bovine aprotinin and 7-26mcg riboflavin, to reduce the rate of peritoneal adhesion formation in an in-vivo model.

Animal-derived and recombinant collagens, especially type I represent one of the most useful biomaterials available, being widely used for tissue engineering, cosmetic surgery, and drug delivery systems. They are used either in their native fibrillar form or after denaturation in variously fabricated forms, such as sponges, sheets, plugs, and pellets. Type I collagen sponges have been used in developing patellar tendons in rabbits under different culture conditions. Collagen sponge was combined with mesenchymal stem cells derived from bone-marrow, proving that the resulted neotissue reached about three-fourth of the mechanical properties of the normal tissue (Awad, 2003; Juncosa-Melvin, 2006; Juncosa-Melvin, 2007; Koide, 2007). Equine and bovine collagen type I was proposed and evaluated as 3D scaffolds for reestablishing the collagen fibrillar structure of the peritoneum or skin, such substitutes being, nowadays, commercialized extensively (e.g., Tutomesh from Tutoplast, Apligraf from Organogenesis, Inc. and OrCel from Ortec Int.) (Chung, 2007; Nair, 2007). The anti-adhesive efficacy of the spongy sheet of collagen-based biomaterial derived from equine tendons was evaluated in animal experiments using Sprague Dawley rats. Under anesthesia, a 1 cm × 2 cm segment of peritoneum was superficially excised from walls, with the cecum being abraded by scraping with a scalpel blade over a 1 cm × 2 cm area. A piece of spongy sheet of collagen was placed on the peritoneal defect, both defects being, consecutively, placed in contact, before the abdominal closure. 7 days after the surgical application of the collagen sponge, the peritoneal condition was evaluated, demonstrating the role of the biomaterial used in the study in facilitating the wound healing of surgically excised tissue and preventing surgically excised tissue from adhering to adjacent structures (Misato, 2014).

The feasibility of using collagen as biomaterials for engineering collagen (type I) tissues in peritoneum, tendon and skin can be ascertained, but, the use of animal-derived products may be compromised by possible allergic reactions and pathogen transmission. Because recombinant collagen does not undergo significant posttranslational modifications, the efficacy of the animal-derived collagen biomaterials may be decreased by the lack of biologic activities of native tissue.

Replicating the nanoscaled structures and the molecular components of native collagen fibrils shed light on the desired bioactivities of those novel biomaterials. Although only oversimplified replicas can be developed currently, they still represent advances in biomaterials engineering and cell biology, even though current application is still at the beginning. The application of biomaterials, such as animal-derived collagen, has provided further insight into biomaterial-cellular interactions, further refinement of current biotechnology being necessary for the evolution of tissue engineering in the future.

To promote further development of tissue engineering and clinical applicability of these products, it is important to optimize fabrication and application that provides satisfactory interaction and imitation of biologic functions.

CONCLUSIONS

Postsurgical adhesion syndrome represents a major health problem with impact on both quality of life and health-care costs. General intraoperative preventative practices such as use of starch-free gloves, avoidance of unnecessary peritoneal dissection, and avoidance of spillage of intestinal contents or gallstones may reduce the risk of adhesions, but the use of adhesion barriers is necessary in high-risk procedures. Equine and bovine collagen type I provides a 3D scaffold for reestablishing the collagen fibrillar structure of the peritoneum, representing an efficient method in the prevention of the postoperative peritoneal adhesions. Animal- derived collagen substitutes used in the prevention of the postoperative peritoneal adhesion syndrome are, nowadays, commercialized extensively. There is still no unequivocally effective adhesion-reducing barrier. Continuing research is needed for the development of more effective products for reduction of adhesions.

REFERENCES

- Awad, H.A. *et al.* (2003), "Repair of patellar tendon injuries using a cell-collagen composite", *The Journal of Orthopaedic Research*, 21, 420–431, [https://doi.org/10.1016/S0736-0266\(02\)00163-8](https://doi.org/10.1016/S0736-0266(02)00163-8).
- Chung, H.J. and Park, T.G. (2007), "Surface engineered and drug releasing pre-fabricated scaffolds for tissue engineering", *Advance Drug Delivery Review*, 59, 249–262, <https://doi.org/10.1016/j.addr.2007.03.015>.
- Coccolini, S. (2013), "Peritoneal adhesion index (PAI): proposal of a score for the "ignored iceberg" of medicine and surgery", *World Journal of Emergency Surgery*, 8, 6, <https://doi.org/10.1186/1749-7922-8-6>.
- Johns, A. (2001), "Evidence-based prevention of post-operative adhesions", *Human Reproduction Update*, 7, 577–9, <https://doi.org/10.1093/humupd/7.6.577>.
- Juncosa-Melvin, N. *et al.* (2007), "Mechanical stimulation increases collagen type I and collagen type III gene expression of stem cell-collagen sponge constructs for patellar tendon repair", *Tissue Engineering*, 13, 1219–1226, <https://doi.org/10.1089/ten.2006.0339>.
- Juncosa-Melvin, N. *et al.* (2006), "Effects of mechanical stimulation on the biomechanics and histology of stem cell-collagen sponge constructs for rabbit patellar tendon repair", *Tissue Engineering*, 12, 2291–2300, <https://doi.org/10.1089/ten.2006.12.2291>.
- Koide, T. (2007), "Designed triple-helical peptides as tools for collagen biochemistry and matrix engineering", *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, 362, 1281–1291, <https://doi.org/10.1098/rstb.2007.2115>.
- Malinak, L.R. and Young, A. (1997), "Peritoneal closure: when and why", *Contemporary Obstetrics and Gynecology*, 42, 102–12.
- MaZuJI, M. and FaDhLI, H.A. (1965), "Peritoneal adhesions; prevention with povidone and dextran", *Archives of Surgery*, 91, 872-874, <https://doi.org/10.1001/archsurg.1965.01320180006002>.
- Misato, K. *et al.* (2014), "Development of anti-adhesive spongy sheet composed of hyaluronic acid and collagen containing epidermal growth factor", *Journal of Biomaterials Science, Polymer Edition*, 25, 13-12.
- Nair, L.S. and Laurencin, C.T. (2007), "Biodegradable polymers as biomaterials", *Progress in Polymer Science*, 32, 762–798, <https://doi.org/10.1016/j.progpolymsci.2007.05.017>.
- Suzuki, Y. and Ikada, Y. (2012), *Biomaterials for Surgical Operation*, Springer Science+Business Media, LLC.
- Tulandi, T. and Al-Jaroudi, D. (2003), "Nonclosure of peritoneum: a reappraisal", *American Journal of Obstetrics and Gynecology*, 189(2), 609–12, [https://doi.org/10.1067/S0002-9378\(03\)00299-0](https://doi.org/10.1067/S0002-9378(03)00299-0).
- Ulandi, T. *et al.* (1988), "Closure of laparotomy incisions with or without peritoneal suturing and second-look laparoscopy", *American Journal of Obstetrics and Gynecology*, 158, 536–7, [https://doi.org/10.1016/0002-9378\(88\)90020-8](https://doi.org/10.1016/0002-9378(88)90020-8).