Biological prosthesis, platelet enriched plasma and bone marrow stem cells in complicated incisional hernia reconstruction in emergency surgery: a prospective case control study

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Abstract

Numerous innovations have been aided by abdominal wall surgical repair. Abdominal wall surgery was drastically altered by synthetic materials. Tissue engineering was unquestionably first applied to biomaterials. The purpose of the present study is to compare different repeating approaches with rising tissue engineering complexity in repairing complex incisional hernia in emergency setting. Patients with complicated incisional hernia were prospectively included in the study and divided into 4 groups: DR (Direct Repair) group underwent direct reconstruction of the abdominal wall, BR (Biological mesh Repair) group underwent reconstruction of the abdominal wall with biological mesh (retro-muscular), BPR [Biological mesh and Platelet Enriched Plasma (PEP), gel] group underwent reconstruction of the abdominal wall with Biological mesh (retro-muscular) and PEP, BPSR (biological mesh, PEP gel and Bone Marrow Stem Cells) group underwent reconstruction of the abdominal wall with biological mesh (retro-muscular), PEP and Bone Marrow Stem cells (BMSc). Forty patients were enrolled. Patients in the DR group experienced a higher rate of severe complication ($p<0.05$). Recurrence rates were 60% for DR patients, 20% for BM patients and 10% for the BM+PEP group ($p<0.05$). Median follow-up period was 64.6, 55.7 and 55.8 months ($p<0.05$). 7- and 30-days abdominal wall thickness is progressively increased by different techniques: BP, BP+PEP and BP+PEP+BMSc ($p<0.05$). No mortality was registered. Tissue engineering techniques in abdominal wall reconstruction showed promising results. They seem to reduce the recurrence rate without increasing complication one in complicated incisional abdominal wall hernia. Although many aspects are yet to be determined and standardized, it seems extremely important to continue research and experimentation in this field.

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Introduction

Major surgery frequently results in an Incisional Hernia (IH), particularly when performed in an emergency situation with a contaminated or infected surgical field. The incidence of IH in patients operated with peritonitis is up to 54%, compared with an incidence of 11–26% in the general surgical population.[1-3] Abdominal wall defect repair is widely diffused and practiced. Several materials are used, with synthetic non-absorbable materials being the most popular. Biological materials are also utilized and brought good results. Indications about their use and usefulness in infected fields have been published by the Italian Biological Prosthesis Working Group.[4] However, abdominal wall and his function is generally considered to be less important than that of the nearby abdominal organs. For this reason, there is typically little mainstream research conducted to improve surgical techniques addressing abdominal wall repair. The advent of Synthetic Materials (SM) before, and the Biomaterials (BM) after, has deeply changed the abdominal wall surgery.[5] However, it presented a series of new and sometimes challenging situations to deal with (*i.e.*, prosthesis infection, mesh implant in contaminated/infected fields, adhesions risk, fistula). On the other hand, biomaterials introduced a completely different approach to abdominal wall reconstruction allowing to successfully face complex situations. BM use definitively introduced tissue

engineering into the general surgeon tools.[6-9] These materials combined with patient autologous Platelet-Enriched Plasma (PEP), have the possibility to improve tissue regeneration.[10,11]

The present study aims to compare different repeating approaches with rising Tissue Engineering (TE) complexity in repairing complex abdominal wall defects in emergency setting.

Materials and Methods

Patients with complicated incisional hernias operated in emergency setting have been prospectively included in the study and treated in four groups: i) DR (Direct Repair) group: 10 patients underwent direct reconstruction of the abdominal wall; ii) BR (Biological mesh Repair) group: 10 underwent reconstruction of the abdominal wall with biological mesh; iii) BPR (Biological mesh and PEP gel) group: 10 underwent reconstruction of the abdominal wall with biological mesh and PEP; iv) BPSR (biological mesh, PEP gel and Bone Marrow Stem Cells) group: 10 underwent reconstruction of the abdominal wall with biological mesh, PEP and bone marrow stem cells (BMSc).

Patients with major comorbidities have been excluded (cardiovascular, respiratory, kidney and vascular disease, diabetes, present/past cancer). In all groups, whenever necessary, anterior component separation (complete or partial) to allow anterior fascial closure was performed. Primary closure of the abdomen was done with absorbable interrupted stitches. Biological mesh used were all made by purified cross-linked porcine dermis (Permacol™ Covidien, Dublin, Ireland). In all patients, the mesh was positioned retro-muscular and anchored using non-absorbable transfixes stitches.

Homologous PEP, prepared by the transfusion unit of our hospital, was used. It was gelled in the operating theater by medical and nursing staff specifically trained, and applied within 30 minutes from the activation (gelling procedure is performed by adding to the PEP, on a Petri dish, human thrombin, and gluconate calcium that both activate the thrombin and induces platelet degranulation). The PEP gel was always applied on the biological mesh.

BMSc were withdrawn from bone marrow blood taken intraoperatively from the iliac crest (approximately 100cc); the collected blood is treated with a closed loop mechanism inside the SmartPReP2 system (Harvest, TerumoBCT, Tokyo, Japan). The final product was added to PEP before the beginning of the gelling process to obtain a mechanically stable product. All patients signed an informed consent for both the use of homologous PEP and of autologous transfusion of BMSc. The measured outcomes were mortality (intra-operative, post-operative and 6 months), morbidity, abdominal wall hernia recurrence, thickness of the newly formed wall at 7 and 30 days calculated using the CT-scan.

Postoperative complications were evaluated according to the Dindo-Clavien classification.[12]

The patient's quality of life was evaluated by administering a simple questionnaire on perceived life quality made by 5 questions on a Likert scale of 10 steps responses (0 to 9 where 0 represents the lowest and 9 the highest value). The questions submitted were the following: i) how do you feel physically?; ii) how would you rate your quality of life?; iii) do you believe you improve your autonomy after surgery?; iv) do you think that the result is acceptable from an aesthetic point of view?; v) do you feel pain in contracting the abdominal muscles during daily activities?

Statistical analysis

Continuous variables are expressed as mean (SD) and were compared with the ANOVA test; categorical variables are expressed as percentages and were compared with the Pearson chi square test; follow-up and incisional hernia risk was calculated with the Kaplan-Meyer method and different techniques were compared with paired log rank test; multivariate analysis were calculated with logistic regression method and with the Cox logistic regression method, including only significative variables at the univariate analysis. $p<0.05$ was considered significative. Analysis was calculated using SPSS 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp).

Results

Forty patients were included into the study. Baseline characteristics between groups were homogeneous (Table 1). The mean and median age were respectively 51,5 and 54 (range 16-18). It has been used an average of 5 PEP units (range = 4-7) equal to 25 cc of product. 10 patients underwent direct suture (DR group), 6 (60%) recurred, including a case of evisceration which required a re-intervention. One out of these 6 patients experienced the formation of an entero-cutaneous fistula which required surgery with ileal resection and a new abdominal wall reconstruction. Three patients had partial dehiscence of the surgical wound treated with negative pressure therapy and advanced dressings. The average perceived quality of life was 24/45.

Ten patients underwent abdominal wall reconstruction with biological mesh (BR group), 2 (20%) developed subcutaneous seroma. One of those patients underwent ultrasound guided percutaneous drainage and the other one percutaneous evacuation; 2 patients (20%) recurred with incisional hernia. The average wall thickness was 2,1cm±0.2cm at 7 days and 0.7 cm±0.1cm at 30 days. The average perceived quality of life was 33/45.

Ten patients underwent abdominal wall reconstruction by biological mesh and PEP gel. One patient (10%) developed abdominal wall relaxation without fascial continuity interruption for the poor thickness of the newly formed abdominal wall. Three patients (30%) developed subcutaneous seroma and underwent percutaneous evacuation. The average wall thickness was 2.5 cm±0.22 cm at 7 days and 1.4cm±0.11cm at 30 days. The average perceived quality of life was 37/45.

Ten patients underwent abdominal wall reconstruction with BP, PEP gel and BMSc; none recurred with incisional hernia. One patient (10%) developed subcutaneous seroma and underwent percutaneous evacuation. The average wall thickness was 2.6 cm±0.19cm at 7 days and, at 30 days, ±1.75 cm ±0.12 cm. The average perceived quality of life was 42/45.

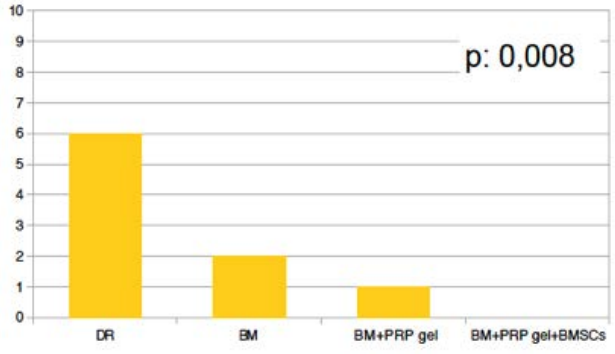

Figure 1. Recurrence rate. PEP, platelet enriched plasma; BMSCs, bone marrow stem cells.

Morbidity analysis showed that there were no significant differences between the different techniques regarding the overall complication rate. However, there is a significant difference between the treatment groups if we only consider the severe complication rate: in fact, patients from the DR group experienced a higher rate of severe complication ($p<0.05$).

The recurrence analysis showed the significant differences between the four groups (Figure 1). Patients from the DR experienced the highest recurrence rate (60%), followed by the BR (20%), the BPR group (10%) and the BPSR group (0%) ($p<0.05$). (Figures 2 and 3) The time of recurrence is influenced by the repairing technique. Mean and median time of recurrence for DR, BR and BPR are respectively 3.1 and 2.8, 62.3 and 64.6, 55.7 and 55.8 months ($p<0.05$).

7- and 30-days abdominal wall thickness is progressively increased by the different techniques: BR, BPR and BPSR ($p<0.05$).

No case of postoperative mortality was registered.

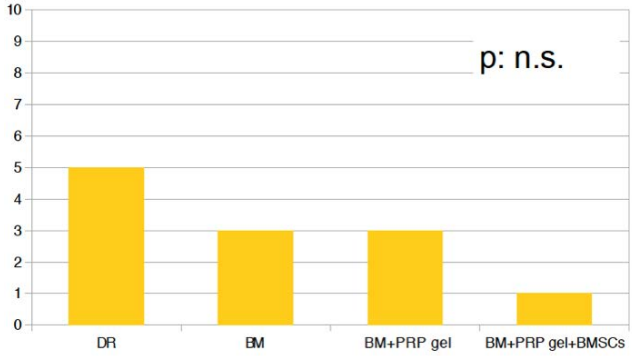

Figure 2. Complication rate. PEP, platelet enriched plasma; BMSCs, bone marrow stem cells.

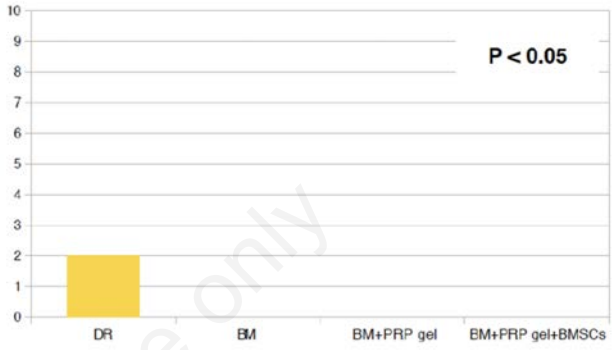

Figure 3. Severe complication rate. PEP, platelet enriched plasma; BMSCs, bone marrow stem cells.

Table 1. Patients characteristics and study outcomes (DR (Direct Repair), BPR [Biological mesh and Platelet Enriched Plasma (PEP), gel], BPSR (biological mesh, PEP gel and Bone Marrow Stem Cells), BMSc (PEP and Bone Marrow Stem cells), SD (standard deviation).

	DR	BPR	BPSR	BMSc	P
Age					
Mean±SD	51,5±15,5	50,4±10,04	52,20±14,25	53,4(±9,857)	n.s.
Median(range)	54(16-68)	48(36-65)	58(29-67)	54(35-68)	
Gender M/F	6/4	5/5	5/5	5/5	n.s.
Hernia dimension					
Mean±SD	Length 6.6±1.9; 6.5(3-10)	Length 10.1±1.4; 10.5(8-12)	Length 8.1±2.5; 8(4-13)	Length 9.1±1.8; 9.5(5-11)	n.s.
Median(range)	Width 18.2±2.7; 18(13-22)	Width 16.2±3.2; 16(11-21)	Width 17.1±3.4; 17(12-22)	Width 17.9±3.2; 16(13-25)	
Abdominal wall Thickness 7gg (cm)					
Mmean±SD	/	2±0	2.4±0.5	2,8±0,4	<0.05
Median(range)	/	2(1.91-2.29)	2(2.29-2.72)	3(2.41-2.76)	
Abdominal wall Thickness 30gg (cm)					
Mean±SD	/	1±0	1,1±0,3	2±0	<0.05
Median(range)	/	1(0.6-0.8)	1(1.3-1.5)	2(1.63-1.82)	
Recurrence	6(60%)	2(20%)	1(10%)	0	<0.05
Time to recurrence (months)					
Mean±SD	3.1±1.3	6.8±0.9	11.03±0.0	/	<0.05
Median(range)	2.8	6.83	55.83	/	
Follow-up					
Mean±SD	34.8±45.6	62.3±40.8	55.7±32.9	45.3±22.01	n.s.
Median(range)	34.7	64.6	55.8	38.8	
Complications	5(50%)	3(30%)	3(30%)	1(10%)	n.s.
Severe Complications*	2(20%)	0	0	0	<0.05
Mortality	0	0	0	0	-
Quality of life score					
Mean±SD	24±3.1	33±6.7	37±5.4	42±2.9	<0.05
Median(range)	24.5(21-29)	35.5(23-41)	37(29-43)	43(37-45)	

Discussion

Incisional hernia is a frequent complication of major abdominal surgery and it occurs in 10–23% of patients undergoing laparotomy,[13] and in almost 50% in case of infected fields.

Several factors affect the process of wound healing: surgical site infection, poor surgical technique, and patient-related factors (*i.e.*, peritonitis, old age, obesity, diabetes mellitus, nutritional deficiencies, hepatic cirrhosis, jaundice, renal impairment, malignancy, cardiac disease, chest problems, previous abdominal incisions, steroid therapy). Nationwide prospective data have shown that in 89% of patients with repair for incisional hernia, the defect was <15 cm (median 7 cm), while in 11% of patients with incisional hernia repairs, the defects were >15 cm. Several surgical techniques are available. They are mainly divided into prosthetic and non-prosthetic ones. With the increase of the defect size, the necessity of prosthesis implantation and associated component separation techniques increase.[14,15] There are 14 studies (1,198 patients) about voluminous incisional hernia, including one randomized trial. Studies were mainly small and retrospective and highly heterogeneous regarding design, outcome, inclusion, and exclusion criteria. The overall median morbidity rate was 32% with a wide range between studies of 4–100%. The mortality ranged from 0 to 5% (median 0%) and recurrence rate ranged from 0 to 53% (median 5%). Study follow-up ranged from 15 to 97 months (median 36 months). According to the literature, mesh repair should always be used for patients undergoing repair for big hernias, and the sublay position may have advantages over onlay positioning.[16-17] To avoid tension, it may be advisable to use a mesh in combination with a component separation technique. Inlay positioning of the mesh and repair without a mesh should be avoided. Evidence to optimize repair for big hernias is weak due to the heterogeneity and the poor quality of the studies. However, sublay positioning of the mesh, perhaps in combination with a component separation technique, may be advantageous compared with other surgical techniques for big hernia repair. Big incisional hernia repair is a challenging surgical procedure and severely lack evidence-based research from high-quality, large-scaled randomized studies. Biomaterials has been progressively more utilized in the last 20 years in repairing voluminous incisional hernias.

The main problem experienced utilizing BM is posed by the very different ways by which such materials can be implanted and implemented. The use of SM stimulates a foreign-body reaction, which facilitates repair of the abdominal wall with scar tissue formation.[6] Conceptually, SM are more like patches used to merely cover a hole while the inflammation process covers them with fibrous tissue, whereas BM, by contrast, could be considered a fundamental component of a complicated TE procedure that will be finally integrated in the newly formed tissue. By using BM, a highly complex cascade of reactions is triggered; this ultimately leads to the complete restoration of the abdominal wall with new, healthy, patient-generated tissue.[6] TE is commonly defined as «an interdisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that aim to maintain, restore, or improve tissue formation»;[6] as such, one of the main objectives of TE is the progressive three-dimensional assembly of vital organ tissue by a process that involves a complex series of cell signaling in the extracellular matrix.[6,8,9]

A description of *in vitro* TE could be simplified to a series of procedures including the inoculation of cells, growth factors, differentiating factors, and other substances inside a biomaterial scaffold to facilitate the growth of a new tissue/organ. *In vivo* TE relies on the body's natural ability to regenerate tissue over non-cell-seeded biomaterials with the possible local inoculation of PEP or BMSc.[6,7,16] The fact that host tissue tends to respond differently to BM depending on the site of implantation (intra- or extra-peritoneal) supports the wide-ranging implications of the use of such materials. The different types of tissue formation that can be stimulated in different regions of the body using the same BM indicates that the host response triggered by the ECM is not the same standardized response caused by SM. The different factors that must be considered during the remodeling process are highly variable.[15,16] It is very important, on this evidence, that surgeons address BM-associated abdominal wall surgery with a more analytical and experimental-oriented mindset. Lastly, it is strongly important to improve a team strategy that involves surgical, biomolecular, and bioengineering sciences. This team strategy will improve the surgeon's ability to consider the biomolecular aspects of surgical procedures and promote a more cohesive synergy to resolve abdominal wall-related health problems that greatly affect a patient's quality of life. Although this treatment should be used only in selected patients because of the high costs and the great technical complexity. The results seem to confirm the literature data although available studies comparable are few and moreover only in animal models.[10-20]

Present results show how the use of different TE parietal reconstruction techniques seems to correlate with a lower incidence of incisional hernia recurrence, a reduction of the postoperative complications rate and an improvement in the perceived quality of life. Moreover, the 7 and 30 days new formed abdominal wall thickness is influenced by the technique. In contrast, the use of such innovative techniques and materials did not show any increase in complication rate. The incidence of severe complications is not significantly incremented by the TE techniques and no death happened in the 4 groups. Furthermore, even though the present study has not analyzed the cost-effectiveness of the proposed model, it could be the subject of future investigation. However, the reduction in recurrence rate could justify the higher initial cost. Moreover, the increase in perceived quality of life represents an associated value of the techniques.

Conclusions

Tissue engineering techniques in abdominal wall reconstruction showed promising results. They seem to reduce the recurrence without increasing the complication rate in complicated incisional abdominal wall hernia. Although many aspects are yet to be determined and standardized it seems extremely important to continue research and experimentation in this field.

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