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The use of RemoweLL oxygenator-integrated device in the prevention of the complications related to aortic valve surgery in the elderly patient: Preliminary results

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Abstract

Background: The effects of fat microembolization due to cardiopulmonary bypass are well known in cardiac surgery. Our aim is to evaluate the use of the RemoweLL device (Eurosets, Medolla, Italy) during elective aortic valve replacement in elderly patients (>70 years old) to rate its biochemical and clinical effects. The RemoweLL device is an oxygenator-integrated reservoir which combines two strategies for fat emboli and leucocytes removal: filtration and supernatant elimination.

Methods: Forty-four elderly patients were enrolled and assigned randomly to a Group A (standard device) and a Group B (RemoweLL). Biochemical effects were evaluated by blood samples, which were tested for white blood cells, neutrophils, protein SP-100 and interleukin 6 besides standard lab tests. Our clinical endpoints were any type of neurological, cardiac, respiratory, gastrointestinal or renal complications, and length of stay in the intensive care unit. Statistical analysis was carried out with chi square test for non-parametric data; *t* test and analysis of variance for repeated measures were used for parametric data.

Results: Group B showed lower levels of white blood cells, neutrophils, interleukin 6 and protein SP-100 immediately and 24 hours after the operation. Group B also showed a lower amount of neurocognitive type II dysfunction even if the length of stay in the ICU did not change.

Conclusions: The RemoweLL system is safe and effective in reducing inflammatory response to cardiopulmonary bypass and it could be a useful tool in minimizing negative effects of cardiopulmonary bypass; however, it does not seem to have any effect on elderly patients' hospital stay.

Keywords

Leucocyte filtration, fat removal, aortic valve replacement, CPB, prevention of neurological complications after valve surgery

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Introduction

Despite recent improvements in cardiopulmonary bypass (CPB) techniques, brain damage still represents a significant cause of morbidity after cardiac surgery. Brooker and his colleagues clearly demonstrated the presence of micro-embolization in brain tissue

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specimens obtained from animal and human corpses[1] and other authors reported the potential role of lipid micro-emboli in damaging other organs, particularly the kidneys and lungs.[2] The effects of this micro-embolization during CPB is clinically evident at the onset of neurocognitive dysfunction in the immediate postoperative period and the incidence of this phenomenon ranges from 6% to 30% according to the present scientific literature.[3,4]

Moreover, CPB induces a systemic inflammatory response syndrome (SIRS) from various mechanisms including the contact between the blood and the surface of the extracorporeal circuit, the operative trauma, the ischaemia–reperfusion injury and the blood–air interface. This inflammatory response involves the activation of several cells and systems, including the complement, the leucocytes and the endothelium. By releasing cytokines, activated leucocytes damage the endothelium, CPB increases vascular permeability and, potentially, contributes to organ dysfunction.[5,6] The shed mediastinal blood is the main suspect as the lipid emboli source and one of the factors responsible for activation of the fibrinolytic and inflammatory cascades.[1] In addition, this phenomenon is stronger in the elderly population and its effects have a greater impact on the postoperative course in this type of patient.[7,8] According to these findings the biomedical industry tried to remedy the problem by developing new devices capable of removing lipid particles and leucocytes from the pericardial shed blood. Several separation strategies are under investigation including particle separation by ultrasound, sedimentation-based separation, and filter strategies.[5,9] The aim of our study is to evaluate the efficacy and the cost effectiveness of a device which combines two different strategies: leucocyte filtration and physiologic fat separation from blood with the creation of a supernatant which is discarded.

The RemoweLeucoLipids (RemoweLL, Eurosets, Medolla, Italy) is an innovative device that contains a filtering layer and supernatant separator designed for both leucocyte removal and lipid filtration. The suction blood passes first through the filter before reaching an internal chamber where the supernatant is sequestered. Some clinical researches on the use of this device are available in the international literature but they, on the whole, concern the application of RemoweLL to coronary artery bypass grafting interventions.[9–11] The aim of the present study was to assess the efficacy of the RemoweLL reservoir (Eurosets, Italy) to remove fat particles and leucocytes from shed mediastinal blood during aortic valve replacement interventions.

Materials and methods

Enrolment and randomization

From January 2010 to August 2011, we prospectively enrolled 44 patients who underwent isolated elective aortic valve replacement (AVR) and were operated with a standard system of reservoir-oxygenator (Medtronic, Minneapolis, USA) (Group A) or with the RemoweLL TM reservoir (Eurosets, Medolla, Italy) (Group B). All patients signed the informed consent forms and the study was approved by the University of Parma Ethics Committee (EudraCT Number 2009-015826-13).

Twenty-two patients were assigned randomly to Group A and the other 22 patients to Group B. A blind allocation using random numbers was made after the patient was deemed to be eligible for entry into the protocol. Inclusion criteria were as follows: age more than 75 years old; severe aortic valvulopathy (isolated severe aortic stenosis, severe insufficiency or mixed aetiology) with indication to AVR. Exclusion criteria were as follows: patients with another cardiac procedure associated to AVR, preexisting renal insufficiency, preexisting cerebrovascular disease and patients with previous cardiac surgery.

In order to assess the biochemical efficacy of this device we obtained blood samples from the central venous line at three different time points:

- Before the beginning of surgery: baseline;
- At the end of surgery: Time 1;
- Twenty-four hours after the end of surgery: Time 2.

These blood samples were tested for: white blood cell count, neutrophil count, platelet count, haematocrit, cholesterol, creatinine, creatine kinase-MB, troponin I, interleukin 6 (IL-6) expressed in pg/ml, protein S-100 expressed in ng/ml.

The plasma obtained to test IL-6 levels was kept in aliquots frozen at 20°C before being tested. IL-6 levels were measured by enzyme linked immunosorbent assay. To sum up, the anti-IL-6 purified monoclonal antibodies (mAb) ENDOGEN were coated as a capture mAb on 96-well flat-bottomed plates (Maxisorp; Nunc, Intermed, Denmark). The detection was achieved using an anti-IL-6 biotinylated mAb (ENDOGEN) followed by detection with streptavidin-peroxidase (Sigma, St. Louis, Missouri, USA). The lowest detectable levels for IL-6 were 10 pg/ml. The plasma C-reactive protein was measured by a high sensitivity nephelometric method on a Behring Nephelometer II analyser (Dade Behring, Newark, Delaware, USA). The plasma obtained to test protein S-100 was evaluated by means of the ELISA method

with the Cobas e411 analyser (Hitachi-Japan) and the reagents by Boehringer-Manheim (Germany).

Our primary clinical endpoints were the following:

- Neurological complications (new onset of stroke, epilepsy, transient postoperative neurocognitive dysfunction or postoperative delirium);
- Cardiac complications (new onset atrioventricular block, peri-operative acute myocardial infarction, major arrhythmias);
- Respiratory complications (lung failure requiring prolonged mechanical ventilation for more than 48 h or requiring tracheostomy);
- New onset of postoperative acute kidney insufficiency using RIFLE criteria;
- New onset of gastrointestinal complications;
- Length of stay (expressed in days) in the intensive care unit (ICU).

Neurocognitive dysfunction was evaluated by using the Mini Mental Status Exam[12] before and 48 h after the operation while postoperative delirium was evaluated by using the Memorial Delirium Assessment Scale[13,14] and considering a cut-off score >14 points.[14]

Anaesthesia protocol

Anaesthesia was induced and maintained using target-controlled infusions of propofol and remifentanil. A full muscle relaxation was achieved with cisatracurium besylate given intravenously before tracheal intubation. An intravenous bolus of 2.5 g of tranexamic acid was administered before the initiation of CPB and repeated after the complete separation from CPB and protamine administration. Before arterial cannulation, full heparinization was achieved with a 300 IU/kg bolus of unfractionated heparin. Boluses of heparin were repeated to keep the activated clotting time >480 s (Hemochron Response Whole Blood Microcoagulation Systems, ITC Medical, San Francisco, California, USA).

Surgery protocol

All the procedures were performed through a standard median sternotomy and CPB instituted by right atrium and ascending aorta cannulation. The extracorporeal circulation management was similar in both groups: an optimal flow rate of 2.4 l/min per m^2 and a mean systemic perfusion pressure of 60 mmHg were maintained during surgery in all patients by way of mild systemic hypothermia (34°C).

All procedures were performed using a Yostra HL-20 roller pump (Yostra, Maquet Cardiovascular, NJ, USA). Phosphorylcholine-coated circuits together with an integrated hollow-fibres oxygenator (A.L.One, Eurosets, Medolla, Italy) were used for all the procedures of Group B. The priming consisted of 1000 ml of normal saline solution with 500 ml of Ringer Lactate Solution and 200 ml of 18% mannitol. Intermittent warm blood cardioplegia was used for myocardial protection. All CPB procedures were conducted in moderate hypothermia (34°C). During CPB, the blood vented from the left ventricle was directly collected into the venous reservoir in both groups while the shed mediastinal blood was aspirated and filtered in the RemoweLL in Group B while in Group A the shed mediastinal blood was reinfused in the standard CPB circuit.

Statistical analysis

All continuous data are expressed as mean ± SD. A sample size calculation was carried out to identify the minimum number of patients to be included in each group: on the basis of the studies by Dell'Amore[9] and Lagny and colleagues[11] we would expect a ratio between the mean values relative to the two groups at Time 1 and Time 2 of about 1.25 with a coefficient of variation of 0.25. A two-sided, two-sample *t*-test with group sample sizes of 21 and 21 achieves 80% power to detect a ratio of 1.250 when the ratio under the null hypothesis is 1.000. The coefficient of variation on the original scale is 0.25. The significance level (alpha) is 0.050. This analysis was performed with NCSS PASS 14 (NCSS, Kaysville, Utah, USA) by using the procedure 'tests of two means using ratios' with a balanced 1:1 design.

The statistical analysis was conducted using the chi square test and Mann–Whitney *U* test for non-parametric data while we used the *t* test for both independent samples and for the repeated measurements for the continuous variables. A repeated measures analysis of variance was also use to analyse continuous variables. A *p* value of 0.05 was statistically considered a significant difference. All data were collected in a single database and analysed using SPSS version 21 software (IBM).

Results

Preoperative data of both groups are shown in Table 1. Both groups did not show any statistical difference. CPB time and Aortic Cross Clamp time were similar between the two groups (Group A *vs.* Group B: 101 min ± 16.157 min and 75.45 min ± 13.703 min; $p = 0.632$, *vs.* 105.82 min ± 44.034 min and 71.86 min ± 21.335 min; $p = 0.51$) The main valvular disease in both groups was isolated aortic stenosis (20 patients in Group A and 20 patients in Group B). Mixed steno-

Table 1. Preoperative data of Group A (Medtronic oxygenator) and Group B (Eurosets oxygenator).

	Group A	Group B	*p* value
Sex (M/F)	9/13	13/9	0,366
Age (mean ± SD)	76.82 ± 4.019	78.27 ± 4.672	0.275
BMI (mean ± SD)	26.27 ± 5.240	27.233 ± 3.501	0.394
BSA (mean ± SD)	1.75 ± 0.198	1.81 ± 0.166	0.261
Hypertension (*n*/total)	19/22	20/22	1.000
Diabetes (*n*/total)	4/22	4/22	1.000
Central neurological dysfunction (*n*/total)	0/22	0/22	–
Critical carotid stenosis[a] (*n*/total)	0/22	1/22	0.334
Extracardiac arteriopathy[b] (*n*/total)	6/22	2/22	0.240
COPD (*n*/total)	4/22	2/22	0.664
Previous PTCA-stenting	4/22	3/22	1.000
Previous AMI	2/22	1/22	1.000
Heart failure	1/22	3/22	0.607
Ejection fraction (mean ± SD)	54.73 ± 10.802	54.91 ± 11.225	0.957
NYHA Class II	3/22	0/22	0.315[c]
NYHA Class III	14/22	16/22	0.315[c]
NYHA Class IV	5/22	6/22	0.315[c]
EUROSCORE II (mean ± SD)	7.14 ± 1.356	7.50 ± 2.110	0.501

[a]Critical carotid stenosis is defined as a mono- or bilateral stenosis greater than 70% of the effective calibre of the carotid artery.
[b]Extracardiac arteriopathy is defined as a critical arterial stenosis in one or more arterial districts different from the carotid district.
[c]Mann–Whitney *U* test.
M/F: male/female; BMI: body mass index; BSA: body surface area; COPD: chronic obstructive pulmonary disease; PTCA: ; AMI: acute myocardial infarction; NYHA: New York Heart Association; PTCA: Percutaneous Transluminal Coronay Angioplasty.

Table 2. Types and mechanisms of aortic disease.

Type of aortic dysfunction	Group A	Group B	*p* value
Aortic stenosis	20/22–50%	20/22–50%	1.000
Aortic insufficiency	0/22	0/22	–
Aortic steno-insufficiency	2/22–50%	2/22–50%	1.000

Table 3. Aetiology of aortic disease in our population.

Aetiology (degenerative/congenital)	Group A	Group B	*p* value
Degenerative	21/22	21/22	1.000
Congenital (bicuspid aortic valve)	1/22	1/22	1.000

insufficiency was present in another four patients (two patients in each group). The aetiology of aortic disease was the degenerative one in the majority of patients even if we also collected two cases of congenital bicuspid aortic valve without aortic dilatation, one case for each group (Table 2 and Table 3). During our study no patient with isolated aortic insufficiency was enrolled.

Our biochemical endpoints (Tables 4 and 5) showed a significant statistical reduction of white blood cells, neutrophils and IL-6 and protein SP-100 respectively at Time 1 and Time 2 between the two groups but we did not find other differences regarding platelets, haematocrit, cholesterol, creatinine levels and myocardial markers in both groups.

Focusing on clinical endpoints (Table 6) we observed the following: 8/22 cases of atrial fibrillation in Group A versus 6/22 in Group B, one case of acute kidney insufficiency requiring haemodialysis in both groups and one case of gastrointestinal complication only in Group A (alithiasic cholecystitis); as a result we concluded that Group A and Group B were similar except for the incidence of transient neurocognitive dysfunction and postoperative delirium, in which Group A showed 10 cases out of 22 (four transient neurocognitive dysfunctions and six postoperative delirium) while Group B showed only one case out of 22 (one case of postoperative delirium). Notwithstanding this difference and the incidence of other postoperative complications, the length of stay in the ICU and in-hospital mortality did not differ between groups (respectively 2.82 ± 2.648 days versus 2.73 ± 2.472 and 0 deaths in both groups).

Table 4. Postoperative results – biochemical values.

Variables	Baseline Group A	Baseline Group B	*p* value	Time 1 Group A	Time 1 Group B	*p* value	Time 2 Group A	Time 2 Group B	*p* value
WBC $\times 10^9$/l	7.577 ± 1.842	6.581 ± 1.558	0.06	10.766 ± 2.312	7.006 ± 1.328	<0.001*	11.828 ± 2.465	8.715 ± 1.262	<0.001*
Neutrophils $\times 10^9$/l	6.062 ± 1.474	5.269 ± 1.244	0.061	8.618 ± 1.849	4.271 ± 0.649	<0.001*	9.462 ± 1.971	5.232 ± 0.760	<0.001*
Platelets $\times 10^3$/l	234.45 ± 75.773	251.5 ± 51.307	0.387	134.36 ± 34.428	126.32 ± 32.113	0.427	143.36 ± 40.741	135.71 ± 35.029	0.511
Haematocrit	0.37 ± 0.041	0.39 ± 0.035	0.35	0.32 ± 0.029	0.32 ± 0.037	0.94	0.32 ± 0.036	0.31 ± 0.054	0.612
Cholesterol mmol/l	4.226 ± 1.130	4.526 ± 0.972	0.35	3.795 ± 0.886	4.239 ± 1.072	0.142	3.657 ± .810	4.139 ± 0.881	0.066
Creatinine µmol/L	73.81 ± 23.340	76.31 ± 25.720	0.71	71.751 ± 20.332	79.681 ± 020.612	0.204	81.13 ± 27.496	89.06 ± 24.723	0.318
CK–MB µg/l	1.402 ± 0.945	2.347 ± 2.688	0.127	22.74 ± 13.550	17.60 ± 7.889	0.131	13.345 ± 6.746	12.493 ± 6.394	0.669
Troponin I µg/l	0.0886 ± 0.225	0.1186 ± 0.431	0.774	2.815 ± 2.2801	2.874 ± 1.564	0.920	2.442 ± 1.981	2.600 ± 1.409	0.761
Interleukin 6 pg/l	3.367 ± 1.940	3.901 ± 2.254	0.405	233.089 ± 102.602	140.327 ± 34.388	<0.001*	179.881 ± 86.590	79.234 ± 44.368	<0.001*
Protein SP-100 ng/l	130.852 ± 148.378	89.980 ± 97.436	0.286	421.192 ± 184.179	247.544 ± 141.420	0.001*	183.900 ± 108.547	130.057 ± 58.079	0.048*

WBC: white blood cells; CK-MB: creatine kinase-MB.
*$p < 0,05$.

Table 5. Repeated measures analysis of variance – *p* values.

Biochemical variables	Time	Device	Time × device
WBC	0.000	0.000	0.000
Neutrophils	0.000	0.000	0.000
Platelets	0.000	0.195	0.185
Haematocrit	0.000	0.255	0.105
Cholesterol	0.000	0.707	0.505
Creatinine	0.007	0.668	0.417
CK-MB	0.000	0.074	0.735
Troponin I	0.000	0.103	0.147
Interleukin 6	0.000	0.000	0.000
Protein S-100	0.000	0.027	0.017

WBC: white blood cells; CK-MB: creatine kinase-MB.

Table 6. Clinical endpoints.

	Group A	Group B	*p* value
Prolonged ventilation >48 h	0/22	0/22	–
Atrial fibrillation	8/22	6/22	0.747
Third degree atrio-ventricular block	0/22	1/22	1.000
Major arrhythmias	0/22	0/22	–
Acute kidney insufficiency	1/22	1/22	1.000
Dialysis	0/22	0/22	–
Gastrointestinal complications	1/22	0/22	1.000
Stroke	0/22	0/22	–
Infections	0/22	0/22	–
Neurological dysfunctions	10/22[a]	1/22[b]	0.004*
Intensive care unit length of stay, days	2.82 ± 2.648	2.73 ± 2.472	0.907
In-hospital deaths	0/22	0/22	–

[a]Four cases of transient neurocognitive dysfunctions, six cases of post-operative delirium.
[b]One case of postoperative delirium.
*$p < 0,05$.

Discussion

The search for the best way to reduce the negative effects of CPB on the human body is far from a definitive response. Multiple devices and pharmacological strategies have been tested until now without any results that encourage a certain type of technique rather than another. All in all, of these issues, mini-extracorporeal circulation circuits, closed systems and cell-saving devices have been introduced into clinical practice with promising results[15,16] and other strategies, such as ultrasonic devices, are under investigation to reduce lipid micro-embolization.[17,18]

Sedimentation-based separation is another promising technique even though it remains a controversial issue: the use of filters with a very small pore diameter can decrease the charge on leucocytes but at the same time it may create other problems such as high resistance in the circuit and the loss of important blood components, including platelets and red blood cells.[19] Moreover, the ideal filter needs a short passage time and good biocompatibility. Ultrasonic and sedimentation methods also have several drawbacks limiting their clinical application.[20,21] The RemoweLL technology combines two different strategies: filtration, which removes leucocytes and larger lipid particles (>40 mm), and sedimentation, which is responsible for smaller lipid particle (10–40 mm) removal. The combination of these two strategies is designed to achieve a synergistic effect, reducing the disadvantages of the individual methods.

In our study, the RemoweLL system has been determined to be capable of reducing by 40% white blood cell levels and by 26% neutrophil levels at Time 1 and Time 2. This result is similar to the findings of Dell'Amore and co-authors[9] and to other studies recently published.[11] In the same way the release of pro-inflammatory cytokines is significantly reduced in Group B (RemoweLL) in contrast with Group A. Unlike the above-mentioned studies we did not register differences between haematocrit, platelets and cholesterol levels; even the release of myocardial necrosis markers looks to be similar. We were unable to count the total number of fat micro-emboli in blood samples and so we turned our attention to the clinical endpoints to evaluate this parameter indirectly; in our opinion the clinical endpoints mentioned above are a good option to evaluate the possible reduction of microembolization or the possible reduction of SIRS effects. Most of the clinical endpoints did not differ in both groups (Table 5) but according to our results the discrepancy between the two groups regarding Neurological Dysfunctions is an evidence of the strong decrease of lipid particles after CPB in Group B, and this correlates with the lower levels of protein SP-100 in this group at Time 1 and Time 2.

We did not find any statistical differences between the two groups in terms of clinical endpoints except for the highest incidence of neurological dysfunction in Group A. In spite of this, the length of stay in the postoperative ICU was similar in both groups without a significant clinical impact on the time of hospitalization or morbidity in the immediate postoperative period.

The RemoweLL System applied to elective AVR in the elderly patient proved to be safe and usable with ease. The biochemical effects we found are comparable to other studies in the scientific literature but we must underline that the large part of these studies are applied to the setting of isolated coronary artery bypass graft operations and not to AVR. Moreover, the difference in the incidence of neurological dysfunctions between the two groups is an interesting clinical result which should encourage the use of fat/leucocytes removal from the CPB circuit during on-pump operations. The main limitation remains the small number of patients enrolled and our inability to measure the number of fat emboli in blood samples.

Longer follow-up studies are necessary to elucidate benefits and adverse effects of this device and the results need to be confirmed by more robust statistical tests on a larger scale and on prospective and randomized studies comparing the RemoweLL System with standard CPB.

Author contribution

MA, GM, NF contributed to conception and design of the study, DCMV, CD, RM, BB, GF, GT contributed to design of the study, MA and NF contributed to acquisition, analysis and interpretation of data, GM contributed to analysis and interpretation of data, MVDC, CD, RM, BB, GF, GT contributed to acquisition of data.

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