Comparison of Efficacy and Safety of Non-Regenerated and Regenerated Oxidized Cellulose Based Fibrous Haemostats

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ABSTRACT

Purpose: Various forms of local haemostats are increasingly used routinely in surgical procedures. Our work is the first comparison of the efficacy and safety of non-regenerated and regenerated oxidized cellulose based fibrous haemostats.

Methods: The haemostatic efficacy and safety of fibrous haemostats based on ONRC and ORC were compared in a randomized multicenter study. The primary endpoint was successful haemostasis within 3 minutes of application and no need for surgical revision within 12 hours after the procedure for recurrent bleeding.

Results: There was a significant difference in the rate of successful haemostasis in 3 minutes that was achieved in 82% and 55% in the ONRC and ORC groups, respectively (confidence interval 99%; p = 0.009). Mean time to haemostasis was 133.9 ± 53.95 seconds and 178.0 ± 82.33 seconds, in the ONRC, and ORC group, respectively (p = 0.002). Revision surgery for re-bleeding was necessary in 0 (0%), and 1 (2%) of patients in the ONRC, and ORC group, respectively. No adverse events were reported.

Conclusion: Fibrous haemostat based on ONRC was non-inferior compared to fibrous haemostat based on ORC when used in accordance with its intended purpose, and was safe and efficient.

KEYWORDS

haemostasis; perioperative bleeding; oxidized cellulose; traumacel

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INTRODUCTION

As the age of the population grows and the results of oncological treatment improve, the number of patients in which a greater surgical resection procedure is necessary for the definitive success of the treatment increases. A large group of patients at risk of greater postoperative blood loss are patients with various types of cancer, indicated for radical surgery, especially patients with very large sometimes benign tumours where non-surgical treatment is not successful. Another group consists of patients indicated for surgical diagnostic intervention. A large group consists of patients after complicated inflammatory diseases such as the lungs and chest cavity, when it is necessary to perform decortication and pleurectomy, often with atypical lung resection. In all these groups of patients, a more demanding perioperative course can be predicted, and in the postoperative period it is necessary to anticipate greater blood losses from multiple non-surgical sources. Therefore, it is advantageous to use topical haemostatic agents and thus eliminate ongoing surgically untreatable bleeding. Various forms of haemostats are used as adjuncts to stop residual capillary bleeding persisting after the use of conventional methods to achieve haemostasis and to prevent postoperative blood loss. It allows the perioperative bleeding to stop, usually within a few minutes.

Topical haemostatic agents based on regenerated (ORC) or non-regenerated oxidized cellulose (ONRC) are available in various forms. Knitted gauze, powder and the newest form – fibrous felt, which is increasingly being used as of late. The fibrous felt allows better shaping and resizing, has better absorbency compared to the knitted gauze and copies the application site better.

Topical haemostats work by swelling into a jelly-like mass after soaking in blood, which helps to form a blood clot. This leads to local haemostasis and control of the bleeding. Unlike haemostatic patches, they do not contain fibrinogen or thrombin, parts of the coagulation cascade, that are associated with the risk of thrombosis (1). When used in adequate amounts, the haemostatic preparation is absorbed with virtually no tissue reaction and no residues. The secondary effect is antibacterial, based on low pH, and inhibits the growth and multiplication of micro-organisms (2, 7).

The vast majority of published works were performed with haemostats based on ORC (2–9). Only few papers describe the effect of ONRC haemostatic gauze (10–14) or felt (15–17) and only one published work compares the effect of ORC and ONRC knitted gauze in a larger group of patients (18). The works published so far show that ONRC has a similar or even superior effect (10, 18).

To date, no study has compared the effect of fibrous felt, the newest form, in a larger group of patients. Our comparative study focused on comparing the effect of the fibrous felt based on ORC and ONRC. In addition, the study included more surgical disciplines to compare the effect on different bleeding tissue types.

MATERIAL AND METHODS

OBJECTIVES

The main objective of the study was to compare the efficacy and safety of non-regenerated and regenerated oxidized cellulose based fibrous haemostat when used in accordance with their intended purpose.

The partial objectives were: to identify any previously unknown side-effects and the monitoring of known side-effects; to identify and analyse potentially newly emerging risks; to confirm the acceptability of the benefit-risk ratio; and to identify any systematic misuse of the device or off-label use of the device in order to verify the correctness of its intended purpose.

The primary endpoint was the successful result of a haemostatic agent: Successful haemostasis within 3 minutes of application and no need for surgical revision within 12 hours after the procedure for recurrent bleeding.

ETHICAL ISSUES

This study was conducted according to the Declaration of Helsinki (52nd WMA General Assembly, Edinburgh, Scotland, October 2000) and approved by the Ethic Committee of the University Hospital Hradec Králové, Czech Republic. Written informed consent was obtained from every patient. All patients enrolled in the study had the option to withdraw from the study at any time.

PATIENTS

A total of 98 patients with diffuse soft tissue, vascular or parenchymal bleeding after conventional surgical haemostatic methods that did not work or are impractical (e.g., ligature, suture, compression, cauterization), were enrolled in the study from May 2020 until December 2020 at the University Hospital Hradec Králové, Czech Republic.

The choice of patients was not limited to a specific surgical procedure or diagnosis, nor to the age of the patients.

USED ORC AND ONRC HAEMOSTATS

Traumacel FAM Trium 5 × 10 cm (BIOSTER, a.s., Veverská Bítýška, Czech Republic) as ONRC based haemostat and Surgicel Fibrillar 5 x×10 cm (Ethicon, LLC, Puerto Rico) as ORC based haemostat were used in this study. ONRC is produced by oxidation of natural cotton, ORC is made by dissolution and extrusion and then oxidation. Under the microscope, the ORC fibres are smooth, while the ONRC fibres are porous and frayed.

The material of both is very soft and it is easy to divide into smaller pieces but at the same time it holds its shape well, so it can be sutured at the application site if needed and can also be easily used in endoscopic or robotic surgery.

OPERATIVE PROCEDURES AND DATA

The study took place in 4 centres: cardiosurgical, surgical, neurosurgical and urological. The centres were elected to cover the widest range of operational services. The clini-

cal study was designed to be prospective, controlled, and randomized.

The efficacy parameters monitored were the time required to achieve haemostasis, the rate of successful haemostasis within 2 minutes and within 3 minutes after administration. As safety parameters, complications during surgery, the necessity of surgical revision within 12 hours after the procedure for recurrent bleeding, and the occurrence of adverse events were chosen.

MEASURES TO MINIMIZE OR ELIMINATE BIAS

Blinding by the examiner cannot be achieved. Medical devices are recognizable by their physical properties. Randomization and objectivity were achieved by adding serial numbers to potential patients for the surgery and assigning which preparation would be administered to subjects with an odd serial number and which preparation would be administered to subjects with an even number was chosen in advance.

STATISTICS

The sample size was calculated based on the data from a previous clinical study that had a similar design. It was a non-inferiority test between two tested comparative haemostatic products based on ORC and ONRC. From this, the number of patients in one arm of the clinical study was calculated to be n = 49.

The clinical study was statistically designed as a test of non-inferiority of ONRC based haemostat compared to ORC based haemostat. The rate of successful haemostasis within 2 and 3 minutes was compared. The non-inferiority margin was set at 10%. The statistical method was an unpaired two-samples t-test of non-inferiority. Statistical differences were considered significant when $P < 0.05$.

RESULTS

There were 98 patients enrolled in the study, of whom 66% were men and 34% were women. The mean age of the patients was 62.5 years, the oldest patient was 85 years old and the youngest 20 years old. Baseline demographic characteristics are summarized in Table 1.

Tab. 1 Demographic Characteristics. SD, standard deviation; PHCCM, possible health complications, comorbidities and medications that may affect the outcome of treatment (for more information, see Table 2).

Characteristic	Traumacel FAM Trium (n = 49)	Surgicel Fibrillar (n = 49)	Total (n = 98)	P-value
Age, mean (SD)	62.31 (14.40)	62.73 (13.69)	62.52 (14.05)	0.882
Sex, n (%)				
Male	31 (63)	34 (69)	65 (66)	0.669
Female	18 (37)	15 (31)	33 (34)	0.669
PHCCM, n (%)	29 (59)	23 (47)	52 (53)	0.312

In total 53% of patients had possible health complications, comorbidities and medications that may have affected the outcome of treatment. Differences between patient groups in this respect were not statistically significant. The overview of health complications, comorbidities and medications that may have affected the outcome of treatment is in Table 2.

Tab. 2 List of PHCCM and occurrence. PHCCM, possible health complications, comorbidities and medications that may affect the outcome of treatment.

	Occurrence
Comorbidities	Tumour (8), ischemic heart disease (5), chronic obstructive pulmonary disease (4), Crohn's disease (3), diabetes mellitus (2), atrial fibrillation (2), infection (2), aortic valve implantation (2), sepsis (1), polytrauma (1), cirrhosis (1), ATR syndrome (1), osteoporosis (1), hepatopathy (1), colostomy (1), phlegmona (1), heart failure (1)
Medications	Anopyrin (19), Godasal (9), Fraxiparin (6), Warfarin/Heparin (6), Tromboxan (2), Eliquis (2), Clexane (1), Brilique (1)
Other complications	Nicotine addiction (3), alcohol addiction (2), obesity (2)

The study covered various types of surgery. In addition to conventional surgery, laparoscopic and robotic procedures were included. The procedures performed in the study population were in the areas of thoracic surgery, vascular surgery, plastic surgery, abdominal surgery, neurosurgery and urology.

The differences in the relative proportions of bleeding from the target bleeding site (TBS) between groups were not significant. We can state that the worse bleeding status in neither of the ONRC or ORC groups could affect the primary endpoint. The proportion of bleeding rates was even in both groups. Most of the patients had mild or moderate bleeding. The list of operative procedures and degree of bleeding from the TBS are summarized in Table 3.

The expected dropout was 10–15% but, there was no dropout from the study. An overview of the number of patients monitored during the study is in Figure 1.

Successful haemostasis within 2 minutes was achieved in 43% and 33% in ONRC and ORC groups, respectively (confidence interval 99%; $p = 0.405$). There was a significant difference in the rate of successful haemostasis within 3 minutes that was achieved in 82% and 55% in the ONRC and ORC groups, respectively (confidence interval 99%; $p = 0.009$). Out of these clinical data it can be stated that the ONRC based haemostat is a non-inferior treatment method compared to the ORC based haemostat.

The mean time to achieve haemostasis (TTH) was 133.90 (SD = 54.95; median = 145.00), and 178.04 (SD = 82.33; median = 180.00) seconds in the ONRC, and ORC group, respectively (a normal distribution can be assumed). The shortest time to haemostasis was 30 seconds in both groups. The longest time to haemostasis was 245, and 350 seconds in the ONRC and ORC group, respectively. Mean TTH was shorter in the ONRC group with statistical significance $p = 0.002$.

Tab. 3 Operative Procedures and Data. SD, standard deviation; TBS, target bleeding site; ORC, oxidized regenerated cellulose; ONRC, oxidized non-regenerated cellulose.

Variable	ONRC (n = 49)	ORC (n = 49)	P-value
Type of intervention, n (%)			
Classic	40 (82)	37 (76)	0.623
Laparoscopic	4 (8)	2 (4)	0.678
Robotic	3 (6)	5 (10)	0.715
Endoscopic	2 (4)	4 (8)	0.678
Area of surgery, n (%)			
Thoracic surgery	20 (40)	20 (40)	>0.999
General surgery	5 (10)	5 (10)	>0.999
Vascular surgery	7 (14)	7 (14)	>0.999
Plastic surgery	7 (14)	7 (14)	>0.999
Neurosurgery	5 (10)	5 (10)	>0.999
Urology	5 (10)	5 (10)	>0.999
Anatomic location of TBS, n			
Thoracic	21	18	0.680
Retroperitoneal / Abdominal	15	12	0.652
Pelvic	1	2	>0.999
Cutaneous / Subcutaneous	6	6	>0.999
Extremities	5	4	>0.999
Degree of bleeding, n			
1 = mild bleeding	24	25	>0.999
2 = moderate bleeding	21	20	>0.999
3 = severe bleeding	4	4	>0.999
4 = life-threatening bleeding	0	0	>0.999
Degree of bleeding, mean (SD)	1.59 (0.64)	1.57 (0.64)	0.878
Other methods used to stop bleeding from TBS, n			
Electrocoagulation	12	19	0.192
Mechanical methods	8	14	0.226
Pharmacological methods	1	0	>0.999
None	30	22	0.156

Revision surgery for re-bleeding was necessary in 0 (0%), and 1 (2%) of patients in the ONRC and ORC group, respectively.

In terms of primary endpoints, as the successful result of haemostatic agent use can be considered: a) successful haemostasis within 3 minutes of application, and b) no need for surgical revision within 12 hours after the procedure for recurrent bleeding. In these terms, a successful result was achieved in 40 (82%), and 27 (55%) patients in the ONRC and ORC group, respectively. Clinical outcomes are summarized in Table 4 and Figure 2.

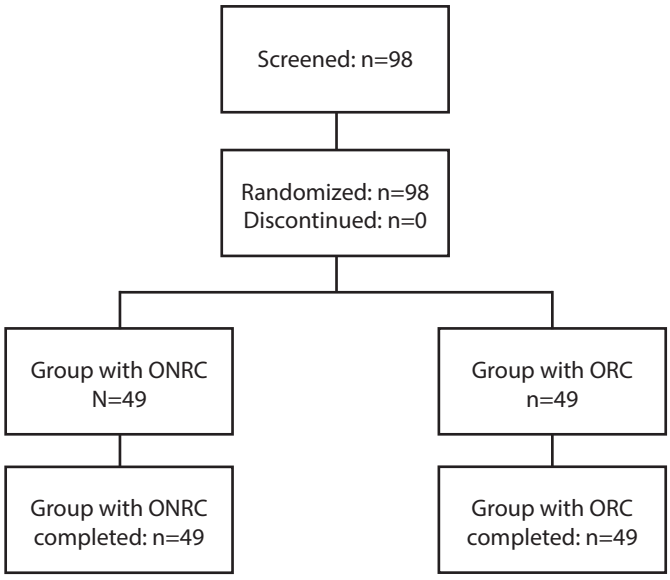

Fig. 1 An overview of the number of patients monitored during the study. ORC, oxidized regenerated cellulose; ONRC, oxidized non-regenerated cellulose.

Tab. 4 Clinical outcomes; SD, standard deviation; TTH, time to haemostasis; ORC, oxidized regenerated cellulose; ONRC, oxidized non-regenerated cellulose.

Clinical parameter	ONRC (n = 49)	ORC (n = 49)	P-value
TTH, mean (SD)	133.90 (53.95)	178.04 (82.33)	0.002
TTH ≤ 120s, n (%)	21 (43)	16 (33)	0.405
TTH ≤ 180s, n (%)	40 (82)	27 (55)	0.009
Revision surgery for rebleeding, n (%)	0 (0)	1 (2)	>0.999

No adverse events (0% [0 of 98]) were reported for either study group both on the surgery day and at a 1-month follow-up. During the follow-up period, there was no reported unscheduled visit (0% [0 of 98]) of patients who underwent the surgery for medical problems, e.g., postoperative complications.

Among patients in the ONRC group, there were no intraoperative or early postoperative complications (0% [0 of 49]). Among patients in the ORC group there were two (4%) complications that were not related to the haemostatic agent. Safety data are summarized in Table 5.

Tab. 5 Safety data. AEs, adverse events; ORC, oxidized regenerated cellulose; ONRC, oxidized non-regenerated cellulose.

Clinical parameter	ONRC (n = 49)	ORC (n = 49)	P-value
Complications, n (%)	0 (0)	2 (4)	0.495
AEs, n (%)	0 (0)	0 (0)	>0.999
AEs at 1-month follow-up, n (%)	0 (0)	0 (0)	>0.999
Unscheduled visits, n (%)	0 (0)	0 (0)	>0.999

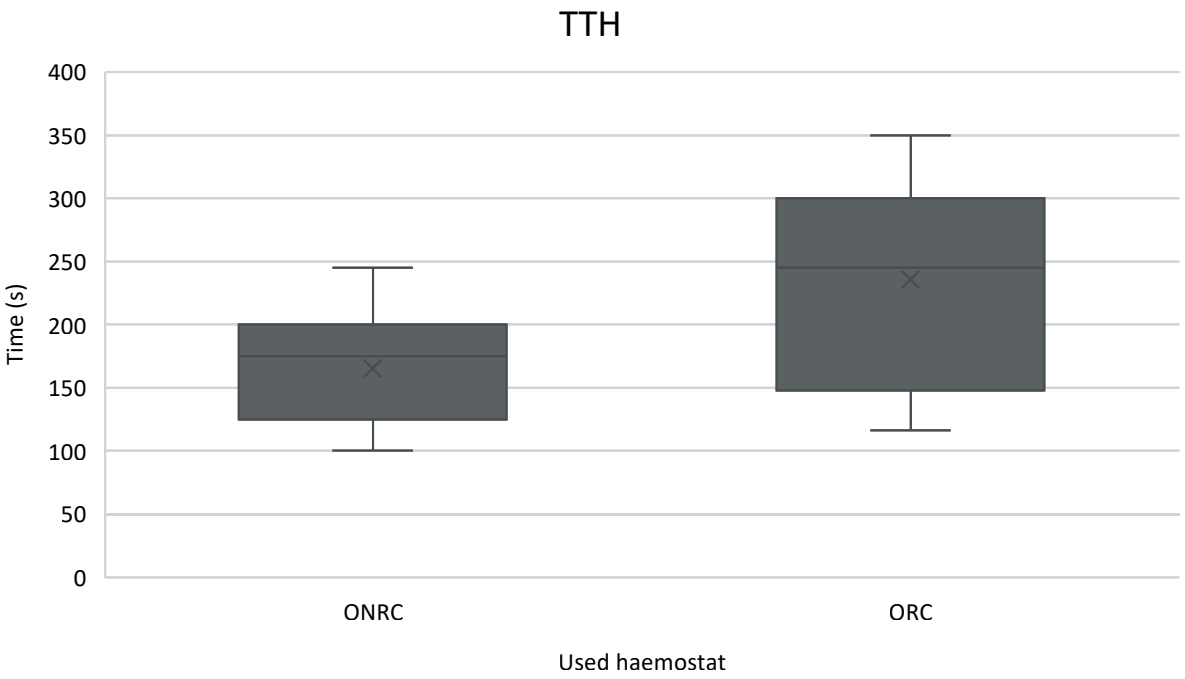

Fig. 2 Time to haemostasis between the ONRC and ORC groups. TTH, time to haemostasis; ORC, oxidized regenerated cellulose; ONRC, oxidized non-regenerated cellulose.

DISCUSSION

The use of local haemostats is becoming increasingly important in connection with the shift of surgical procedures towards more seriously ill patients. In patients with advanced cancer after neoadjuvant chemotherapy, the procedures are usually accompanied by a high number of different complications and a larger number of infectious complications. Decreased immunity of the patient may be involved. These operations have both higher morbidity and mortality.

The reduction of bleeding during the operation and in the postoperative period with the elimination of blood transfers has a positive impact on patients in general, not only those with advanced oncological disease. In the postoperative period, waste of the thoracic drain does not only come from bleeding, but also lymphorrhea, for example after mediastinal or retroperitoneal lymphadenectomy. By applying a local haemostat based on cellulose, we can eliminate this lymph with a good effect. The spectrum of patients is shifting to a higher age group, and this is associated with greater comorbidity. Therefore, the effort to eliminate blood transfusions using local haemostats is playing an increasingly important role.

This study confirms the efficacy and safety of ONRC and ORC haemostats. There was a significant difference in TTH and in the rate of successful haemostasis within 3 minutes in favour of ONRC haemostats. However, this study did not address whether this difference, although significant, was of any clinical significance and therefore could have an impact on the surgeons' decision which haemostat they would use.

The study design also did not consider that the characteristics and severity of bleeding may differ in each type of the surgical procedure, and the efficiency parameters were not evaluated for the individual types of surgery, because this would have required a considerably larger number of patients. This aspect was partially resolved by assessing the degree of bleeding. The numbers of patients with particular bleeding degrees in ONRC and ORC groups were even.

A favourable safety profile has been confirmed in our work thanks to the absence of side effects, dropouts and postoperative complications. Although the absence of dropouts was also due to the fact that all surgical procedures in the study population were planned. Not a single patient experienced an adverse event of any severity, and no haemostat-related complications were reported. From these findings, the high level of safety of both haemostats can be concluded.

However, even in these haemostats, complications may occur in exceptional cases. Several published works describe foreign body reactions with subsequent formation of a granuloma (7). The risk of these complications can be minimized by using the smallest necessary amount of the haemostat.

There have been some previous studies comparing other ONRC and ORC products. A study from 2013 compared the fibre structure, pH in solution, bactericidal effectiveness, and haemostatic effectiveness of an ONRC haemostat and an ORC haemostat. ORC pH was statistically more acidic than ONRC in a phosphate buffer solution, but equal in plasma. No difference in bactericidal effectiveness was observed. In vivo, ONRC provided superior time to haemostasis relative to ORC in the general surgery model; and superior haemostatic success relative to ORC at 30 (60% vs. 15%), 60 (85% vs. 37.5%), and 90 seconds (97.5% vs. 70.0 %) in the peripheral vascular model (10). In 2021 one work was published involving the results of a clinical trial comparing the effectiveness of knitted forms of ORC and ONRC in patients undergoing hepatic resection. There was no significant difference between the ORC and ONRC

groups in time to haemostasis, and there were no differences in the rates of haemostatic success between the 2 groups at 120 seconds (18.4% vs. 24.3%) and 300 seconds (71.1% vs. 89.2%). However, the ONRC group was superior to the ORC group in haemostasis according to the survival analysis (log-rank test, P = 0.044). Moreover, there were also no significant differences between the 2 groups in postoperative drainage volume on the first 2 days and hospital stay (9). So far, all these published clinical data comparing the effectiveness of ORC and ONRC involved knitted haemostats (18).

Given the current trend of fibrous haemostats, which are produced by a technology different from knitted forms, it was good to compare the effectiveness of fibrous haemostats ORC and ONRC.

The new data documenting the use of fibrous ONRC and ORC haemostats gained in our study will be a beneficial contribution to existing knowledge in this area and confirm that ONRC haemostats are non-inferior to ORC haemostats when used according to their current intended use.

CONCLUSION

After a statistical assessment of the clinical data obtained from the study, it is evident that a fibrous haemostat based on ONRC was non-inferior compared to a fibrous haemostat based on ORC when used in accordance with its intended purpose, and that it is safe and efficient.

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Conflict of Interest: P. Habal, MD confirms that there are no conflicts of interest associated with this publication. V. Sívková is an employee of BIOSTER, a.s., P. Votava is an employee of Porta Medica, s.r.o.

ABBREVIATIONS

ONRC oxidized non-regenerated cellulose
ORC oxidized regenerated cellulose
TTH time to haemostasis

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