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Review Article

Concise Review On Clinical Performance Of Oxidized Regenerated Cellulose And Oxidized Non-Regenerated Cellulose – The Better In Cellulose Based - Haemostats

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ABSTRACT

Oxidized Regenerated Cellulose (ORC) undergoes the first step in manufacturing i.e. Regeneration processes of Cellulose prior to Oxidation. Regeneration provides 100% pure cellulose prior to oxidation of ORC, and hence high level of biocompatibility when used as haemostat. Regeneration provides smoothness and pliability, an important handling characteristic, whereas Oxidized Non Regenerated Cellulose (ONRC) will be coarse and will not have pliability to conform to the tissue as evidenced with ORC. ORC can be trimmed to fit any size without fraying compared to ONRC fibre structure which is more sprayed and trimming causes further fraying. Regeneration provides enough Degree of Polymerization (DP) that gives structural integrity and consistency which is not evident in OC. DP in Regeneration processes provides defined and required primary hydroxyl groups (-OH) to get converted to carboxylic acid (-COOH) for the haemostatic and antibacterial – pH, during succeeding step of oxidation. ORC has adequate pH (3-4) to render optimal haemostatic and antibacterial activity without inactivating thrombin, topical agents and drugs. ONRC with its very low pH (1-2) has the potential danger of inactivation. Hence in the present study we analyse and infer that ORC benefits and clinical performance outweigh the ONRC as haemostat in various clinical applications.

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INTRODUCTION

Regeneration of Cellulose

Cellulose is a long chain polymer of glucose molecules, and it is the most abundant organic compound on Earth. It is a key structural component in the cell walls of plants, providing rigidity and strength. In recent years, there has been growing interest in using cellulose for a variety of applications, including in the development of sustainable materials and biofuels. [1]

One process for the regeneration of cellulose involves the use of ionic liquids. Ionic liquids are salts that are liquid at room temperature and have unique solvent properties. They can dissolve cellulose and allow it to be processed into a variety of materials. The cellulose can be dissolved in the ionic liquid and then regenerated by adding a solvent, such as water or ethanol. The regenerated cellulose can then be used to create films, fibres, and other materials. [2]

Another process for the regeneration of cellulose involves the use of enzymes. Cellulases are enzymes that break down cellulose into its constituent glucose molecules. By treating cellulose with cellulases, it can be broken down into glucose, which can then be fermented into biofuels or other products. This process is being explored as a potential method for producing biofuels from non-food crops, such as switch grass or agricultural waste. [3, 4]

A third process for the regeneration of cellulose involves the use of bacteria. Some bacteria are able to produce cellulose as part of their natural metabolic processes. By culturing these bacteria in a controlled environment, large quantities of cellulose can be produced. This process is being explored as a method for producing sustainable materials, such as biodegradable plastics, from cellulose. [4, 5]

Regeneration of cellulose is an important area of research, with potential applications in a wide range of fields, from materials science to biofuels and biotechnology, Pharmaceutical and Medical Device fields.

Important methodologies of Regeneration of Cellulose

Process involving ionic liquids:

Cellulose is obtained from plant material and processed into a suitable form for regeneration. The cellulose is dissolved in an ionic liquid at elevated temperatures and pressures. The cellulose-ionic liquid solution is then cooled and a solvent, such as water or ethanol, is added to the solution. The solvent causes the cellulose to precipitate out of the solution in the form of a gel. The gel is washed and dried to remove any remaining ionic liquid and solvent. The resulting regenerated cellulose can be used to create a variety of materials, such as films, fibres, and other products.

Process involving enzymes:

Cellulose is obtained from plant material and processed into a suitable form for enzymatic treatment. Cellulases are added to the cellulose and allowed to react for a specific period of time. The cellulases break down the cellulose into its constituent glucose molecules. The glucose can be further processed into biofuels or other products, such as bioplastics, biomaterials.

Process involving bacteria:

Bacteria capable of producing cellulose are cultured in a controlled environment. The bacteria are fed a suitable nutrient source to promote cellulose production. The resulting cellulose is harvested and purified. The purified cellulose can be used to create a variety of materials, such as biodegradable haemostats.

Preparation of Oxidized Non Regenerated Cellulose (ONRC):

ONRC is typically prepared by treating cellulose with a strong oxidizing agent, such as sodium hypochlorite (NaClO), to introduce carboxyl groups onto the cellulose chains. The most common method for preparing OC is the Cotton Effect method, which involves the following steps:

- Dissolving cellulose: Cellulose is first dissolved in an alkaline solution, such as sodium hydroxide (NaOH), to form a viscous solution.

- Oxidation: The viscous cellulose solution is then treated with a strong oxidizing agent, such as NaClO, at a controlled temperature and pH. The oxidation process introduces carboxyl groups onto the cellulose chains, which makes the cellulose more hydrophilic and increases its surface area.
- Neutralization and washing: The oxidized cellulose is then neutralized with an acid solution, such as hydrochloric acid (HCl), to remove any excess oxidizing agent. The OC is then washed with water to remove any remaining impurities.
- Drying: The final step is to dry the oxidized cellulose. It can be dried by a variety of methods, including air drying, freeze-drying, or spray-drying.

The degree of oxidation and the carboxyl content of the resulting oxidized cellulose can be controlled by adjusting the concentration of the oxidizing agent and the reaction conditions, such as temperature and pH. The resulting OC product can be further processed into various forms, such as gauze, pads, films, or powders, for use as a hemostatic agent.

Advantages of Regeneration of Cellulose:

Regeneration of cellulose has several advantages such as

- Versatility: Regenerated cellulose can be used for a variety of applications, such as textiles, packaging, biomedical devices, and electronics, among others.
- Biodegradability: Regenerated cellulose is biodegradable and can decompose in natural conditions, which makes it an attractive alternative to synthetic materials that can persist in the environment for decades or even centuries.
- Strength and durability: Regenerated cellulose can be engineered to have high strength and durability, making it suitable for applications that require these properties.
- Cost-effective: The regeneration of cellulose from waste sources is often a cost-effective process that can compete with the production of synthetic materials.
- Health and safety: Regenerated cellulose is generally considered safe for human contact and does not pose a risk to health or the environment.
- Environmental sustainability: Cellulose is the most abundant biopolymer on earth, and its regeneration from waste sources such as paper, cotton, and agricultural residues can reduce the amount of waste in landfills, and thus, contribute to environmental sustainability.

The regeneration of cellulose offers a sustainable and versatile solution for the production of materials with desirable properties, while reducing waste and environmental impact.

Cellulose has been widely used as a raw material for developing hemostatic agents due to its biocompatibility, biodegradability, and excellent hemostatic properties. The design inputs for cellulose as a raw material for regeneration as a hemostat include the following which are more linked to regeneration process

The Clinical Perspectives of ORC and ONRC:

Petr Habal *et al* in 2022 compared the Efficacy and Safety of Non-Regenerated and Regenerated Oxidized Cellulose Based Fibrous Haemostats. It was observed that 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.

Chengshuo Zhang *et al* in 2020 evaluated the effects of 2 different hemostatic agents for the treatment of local bleeding in patients undergoing hepatic resection. This was a monocentric, parallel-group, randomized, and controlled clinical trial to compare oxidized regenerated cellulose gauze (ORCG) with oxidized non-regenerated cellulose gauze (ONRCG) in patients undergoing hepatectomy. The primary endpoint was the time to hemostasis at the target bleeding site. The secondary endpoints were the postoperative drainage volume on the first 2 days after surgery and the hospital stay.

There was no significant difference between the ORCG and ONRCG groups in time to hemostasis from column analysis (238.8 ± 121.6 seconds vs. 193.7 ± 85.3 seconds, P = 0.068), and there were no differences in the rates of hemostatic success between the 2 groups at 120 seconds (18.4% vs. 24.3%; odds ratio [OR], 0.703; 95% confidence interval [CI], 0.231–2.136) and 300 seconds (71.1% vs. 89.2%; OR, 0.298; 95% CI, 0.085–1.041). However, the ONRCG group was superior to the ORCG group in hemostasis 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 (P = 0.436, P = 0.381) and hospital stay (P = 0.537, P = 0.200). ONRCG was not inferior to ORCG as a hemostatic agent in patients undergoing liver resection.

Another *in-vitro* study (K. M. Lewis 2013) was conducted on the fiber structure, pH in solution, bactericidal effectiveness, and hemostatic effectiveness of an oxidized non regenerated cellulose (ONRC; Traumastem) and an oxidized regenerated cellulose (ORC; Surgicel-Original). Fiber structures were compared using scanning electron microscopy, pH of phosphate buffer solution (PBS) and human plasma were measured after each cellulose was submerged, and bactericidal effect was measured by plating each cellulose with four bacteria. In vivo, time to hemostasis and hemostatic success were compared using a general surgery non heparinized porcine liver abrasion model and a peripheral vascular surgery heparinized leporine femoral vessel bleeding model. It was concluded that ONRC provides superior hemostasis and equivalent bactericidal effectiveness relative to ORC, which is likely due to its fiber structure than acidity.

There were studies conducted on oxidized cellulose versus oxidized regenerated cellulose micro particles with various oxidation degree were produced and characterized. Comparative studies were conducted in terms of bactericidal and hemostatic efficiencies in addition to cytotoxicity. The results indicated oxidation levels are not directly dependent on the reaction period. Moreover, regenerated or non-regenerated case is also a factor affecting oxidation degree. Bactericidal activity of both samples was found to be similar. Considering haemorrhage and cytotoxicity findings, regenerated cellulose should be preferred for clinical use. This study shows the importance of regeneration and oxidation degree of cellulose for biomedical use and the results suggest both characteristics should take into consideration in clinical use.

In a study two haemostats oxidized regenerated cellulose (ORC, TABOTAMP) and oxidized non-regenerated cellulose (ONRC, RESORBA CELL) were evaluated on influence local cellular behavior and contraction of the extracellular matrix (ECM). Human stromal fibroblasts were inoculated in vitro with ORC and ONRC. Cell proliferation was assayed over time, and migration was evaluated by Live Cell imaging microscopy. Fibroblasts grown in collagen-gels were treated with ORC or ONRC, and ECM contraction was measured utilizing a contraction assay. An absolute pH decline was observed with both ORC and ONRC after 1 hour. Mean daily cell proliferation, migration and matrix contraction were more strongly inhibited by ONRC when compared with ORC ($p < 0.05$). When control media was pH lowered to match the lower pH values typically seen with ORC and ONRC, significant differences in cell proliferation and migration were still observed between ONRC and ORC ($p < 0.05$). However, in these pH conditions, inhibition of matrix contraction was only significant for ONRC ($p < 0.05$).

ONRC inhibit fibroblast proliferation, migration and matrix contraction, and stronger inhibition of these essential cellular processes of wound healing compared with ORC.

DISCUSSION:

In most of the clinical and *in-vitro* studies ORC was proved to be superior or equivalent to ONRC in hemostatic properties and antibacterial activity. However, ONRC inhibits fibroblast proliferation, migration and matrix

contraction, and stronger inhibition of these essential cellular processes of wound healing which were evidently observed for ONRC when compared with ORC. ONRC has direct effect on wound healing properties though functionally it may be non-inferior to ORC as a Hemostat.

Regeneration processes of cellulose offer several advantages over oxidized ONRGC as a hemostatic agent.

1. Purity: Regenerated cellulose is typically of higher purity than oxidized cellulose. This is because the regeneration processes remove impurities and residual chemicals that can be present in ONRC.
2. Biocompatibility: Regenerated cellulose is more biocompatible than oxidized cellulose. This is because oxidized cellulose contains carboxyl groups that can cause an inflammatory response in the body.
3. Hemostatic activity: Regenerated cellulose has higher hemostatic activity than oxidized cellulose. This is because the regeneration processes create a material with a higher surface area, which enhances its ability to promote blood clotting.
4. Degradation: Regenerated cellulose degrades faster than oxidized cellulose. This is because the regeneration processes create a material with a more amorphous structure, which makes it easier for enzymes in the body to break it down.
5. Consistency: Regenerated cellulose has a more consistent and uniform structure than oxidized cellulose. This is because the regeneration processes create a material with a well-defined structure, whereas oxidized cellulose can vary in structure depending on the method of oxidation used.

Advantages of Regeneration processes of ORC Vs ONRC are presented in Table 1.

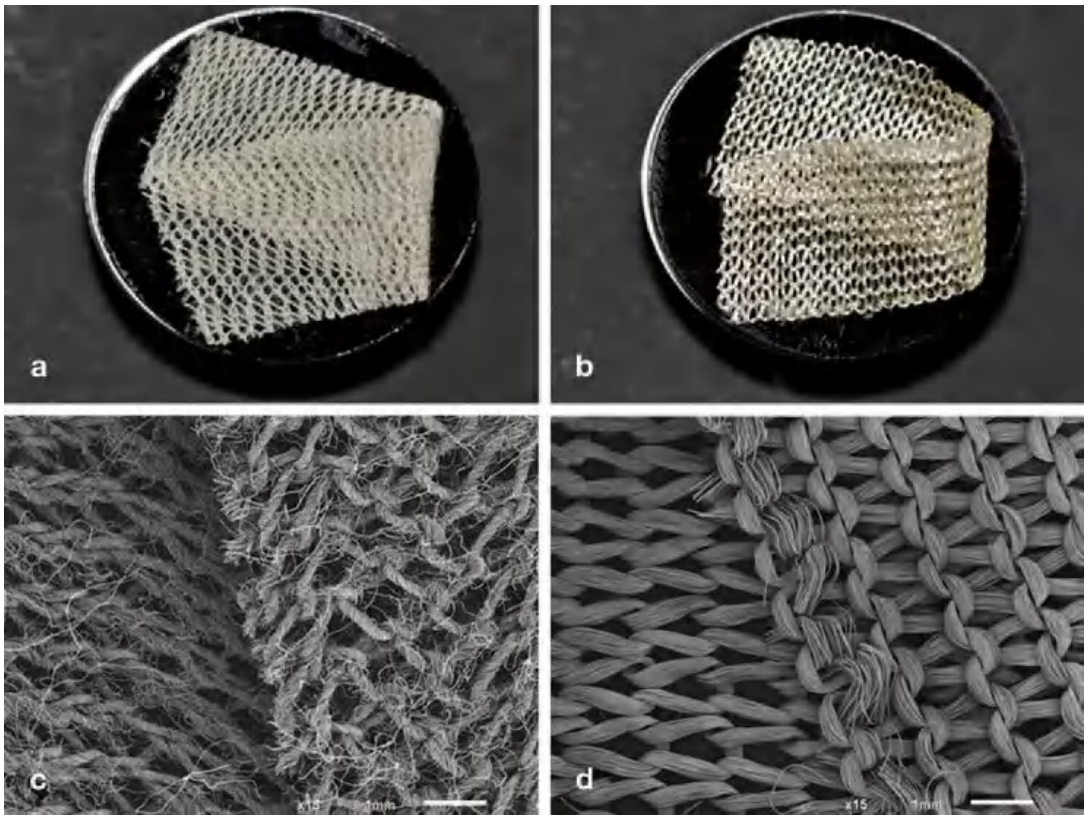
Table 1: The advantage of Regeneration processes of the Cellulose – ORC Vs ONRC

Sr. No	Oxidized Regenerated Cellulose (ORC)	Oxidized Non Regenerated Cellulose (ONRC)
1	Regeneration provides 100% pure Cellulose prior to oxidation of ORC, and hence High Level of Biocompatibility	There is no Regeneration, hence OC will not have 100% purity and may lead to biocompatibility issues
2	Regeneration Induces enough modulus and tensile strength needed for the Haemostat for better conformity and also aids in stitching.	Oxidized Cellulose will not have required tensile strength needed for the Haemostat as compared to ORC
3	Regeneration provides smoothness and pliability, an important handling characteristic of the haemostats (Will be held firmly against bleeding tissue until hemostasis is achieved)	Oxidized cellulose will be coarse and will not have pliability to conform to the tissue as evidenced with ORC
4	Can be trimmed to fit any size without spraying	Non- Regenerated Oxidized cellulose fibre structure is more sprayed and trimming causes further spraying
5	Regeneration provides enough Degree of Polymerization (DP) that gives structural integrity and consistency	There is no Regeneration processes and hence the haemostats will lack structural integrity, consistency and will have instability
6	DP in Regeneration processes provides required Primary hydroxyl groups (- OH) to get converted to Carboxylic acid (- COOH) for the haemostatic and antibacterial – pH, during succeeding step of Oxidation	As there is no Regeneration processes there will be inconsistency in availability of hydroxyl groups (- OH) and conversion to Carboxylic acid (- COOH) during oxidation which will result in varied pH levels and non-uniformity in Hemostasis and antibacterial activity

7	ORC has adequate pH (3-4) to render optimal haemostatic and antibacterial activity without inactivating thrombin, topical agents and drugs	Non- Regenerated Oxidized cellulose with its very low pH (1-2) has the potential danger of inactivation of in vivo thrombin and other topical agents and drugs
8	ORC will not have any effect on wound healing processes. (No effect on the fibroblast proliferation, migration and matrix contraction)	Non- Regenerated Oxidized cellulose will affect the fundamental processes of wound healing and delays healing processes (Non- Regenerated Oxidized cellulose inhibit fibroblast proliferation, migration and matrix contraction, and stronger inhibition of these essential cellular processes of wound healing)
9	The antibacterial activity of ORC against antibiotic resistance organisms is well studied and clinically proven -	Though Oxidized cellulose has antibacterial activity but its activity against antibiotic resistance organisms is not studied and elucidated
10	ORC has quick and sustained hemostasis and low Rebleeding rates	Non- Regenerated Oxidized Cellulose has quick but not sustained hemostasis and issues of Rebleeding

Fig. 1: Actual and Microscopic structure of ORC (b, d) and ONRC (a, c)

Image- Courtesy: Comparison of regenerated and non-regenerated oxidized cellulose haemostatic agents, K. M. Lewis · D. Spazierer · M. D. Urban · L. Lin · H. Redl · A. Goppelt, Eur Surg (2013) 45:213–220, DOI 10.1007/s10353-013-0222-z



CONCLUSION:

In general, oxidized Non Regenerated Cellulose (ONRC) has been used as a hemostatic agent for many years and has proven to be effective in controlling bleeding. However, regeneration processes of cellulose, such as the organic acid regeneration process and the ionic liquid regeneration process and

further oxidation (ORC), offer several advantages over ONRC, including higher purity, better biocompatibility, higher hemostatic activity, faster degradation, and more consistent structure. ORC has not shown any inhibition on wound healing characteristics as compared to ONRC.

For the above reviews it can be concluded that the clinical performance and the benefits of ORC outweigh that of ONRC and ORC can be considered as a better Hemostat than ONRC.

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CONFLICT OF INTEREST:

The Authors have no conflict of interest with any institution, publication or patents

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