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## The use of haemostatic agents in thyroid surgery: efficacy and further advantages. Collagen-Fibrinogen-Thrombin Patch (CFTP) versus Cellulose Gauze

*AIM: To assess the efficacy of two widely used topical haemostatic agents: oxidised regenerated cellulose gauze and Collagen-Fibrinogen-Thrombin Patch in patients undergoing total thyroidectomy.*

*MATERIAL OF STUDY: This was a prospective, comparative, non-randomised study in which consecutive patients undergoing total thyroidectomy for benign disease received standard treatment with no haemostatic agent, cellulose gauze, or CFTP. Main outcome measures were drainage volume 24 hours after surgical procedure and the occurrence of post-operative complications (haematoma, seroma, surgical-site infection).*

*RESULTS: Two hundred seventy-one (271) patients undergoing total thyroidectomy for benign disease: 65 received standard treatment, 60 received cellulose gauze and 146 received CFTP. Seroma was significantly reduced in the CFTP group compared with both the cellulose gauze group ( $p=0.006$ ) and the standard treatment group ( $p=0.017$ ). A significant reduction in drainage volume was also observed with CFTP compared with the other two groups (both  $p<0.001$ ). Drainage volume was also significantly reduced with cellulose gauze versus standard treatment ( $p<0.001$ ). No septic events were observed after application of CFTP. One hematoma was observed in the non haemostatic group.*

*CONCLUSIONS: Both haemostatic agents reduced the amount of sero-hematic fluid during the first 24 hours post-surgery, with CFTP more effective than oxidized cellulose gauze. The use of haemostatic agents may increase the quality of thyroid surgery, improve patient comfort after surgery, and reduce hospital stay.*

**KEY WORDS:** Surgical haemostasis, Thyroidectomy.

### Introduction

Post-thyroidectomy complications, such as vocal cord palsy, permanent hypoparathyroidism, and neck hematoma

can result in severe and even life-threatening injuries, and thus constitute a major concern for surgeons<sup>1,2</sup>. Post-operative hemorrhage may result in airway compression and respiratory distress, most often as a result of laryngopharyngeal edema secondary to the impairment of venous and lymphatic drainage<sup>3</sup>. This phenomenon is caused by blood collecting in a narrow space, which can make tracheal intubation, often necessary to ensure the patient's survival, impossible to perform. The incidence of compressive hematoma after thyroidectomy is reported in the literature as between 0.5% and 4.3%, with an average occurrence of around 1%<sup>2,4,5</sup>. Effective

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hemostasis is an important goal in thyroid surgery, and can reduce the risk of post-operative complications. Various haemostatic techniques and devices are used, including sutures, ligation, clips, and monopolar and bipolar diathermy. In addition, various topical haemostatic agents and tissue adhesives can be used. Haemostatic products that are available in our operating room include an equine collagen patch coated with human fibrinogen and human thrombin (CFTP), and oxidised regenerated cellulose gauze. Although widely used, evidence of the efficacy of these products in thyroid surgery is limited. The purpose of this prospective study was to assess and compare the haemostatic efficacy of CFTP and cellulose gauze in patients undergoing thyroidectomy, in terms of blood loss and the incidence of hemorrhagic events. In addition, we also investigated whether the use of these products was associated with other potential benefits.

## Materials and methods

Between June 2006 and May 2009, we performed a prospective, non-randomized, comparative study involving 271 consecutive patients who were scheduled for total thyroidectomy at our surgical unit. Patients were eligible if they had a preoperative diagnosis of benign thyroid disease, with no signs of malignancy. Exclusion criteria were a diagnosis of malignancy with need for lymph node dissection; sub-sternal goiter; abnormal coagulation or drugs that could interfere with hemostasis. Patients were divided into three groups. Patients in Group A (65) underwent standard thyroidectomy (total thyroidectomy), with extremely careful attention paid to hemostasis and drainage placement, but no additional haemostatic product. Patients in Group B (60) underwent a similar procedure, but with the addition of an oxidized, regenerated, cellulose gauze, which was placed in the thyroid cavity to cover the trachea and lateral spaces containing laryngeal nerves, parathyroid glands, and vessels legated during thyroidectomy. Patients in Group C (146) also underwent the same standard surgical procedure, but with the application of a medicat-

ed collagen sponge coated with human fibrinogen and thrombin. The patch could be applied intact, cut into smaller pieces (5-15 mm<sup>2</sup>), or rolled-up. Areas at risk (e.g., above perineural vessels) were always carefully covered. We preferred use CFTP intact, applying two small parts near the entrance of recurrent nerve. All three groups were comparable in terms of patient characteristics and thyroid volume (Table I). The thyroid size was calculated preoperatively using the following ultrasound criteria:  $ld \times td \times th \times 0.5$  ( $ld$  is the longitudinal diameter of the lobe,  $td$  the transverse diameter,  $th$  the lobe thickness, and 0.5 is a correction factor used to transform the obtained amount from a parallelepiped into an ellipsoid). The calculation of the lobe size was done separately, and the values were added up later. Patients were allocated to groups arbitrarily and/or depending on the availability of tools. Allocation was established by the surgical team at the beginning of each operation. Patients were blinded to their group assignment. All patients were operated on by the same surgical team (two of three surgeons, experienced in endocrine neck surgery: G.G., G.S. and N.C.P.). During the trial, a firm evidence suggested that CFTP was advantageous in reducing drainage volume, so patients enrolled in the CFTP group were much more numerous compared with the other two arms of the study.

Informed consent was provided by all patients, and no patient refused to be recruited for the study. Institutional Ethics Board approval was obtained. All patients underwent open total thyroidectomy, with an incision size, as required, between 25 and 45 mm; conventional total thyroidectomy infact requires an incision size of 40-50 mm. Traditional surgical procedures were carried out with hemostasis achieved by monopolar coagulator and knot-tie technique. Near areas at risk for recurrent nerve or parathyroid damage, bi-polar coagulation was applied only if ligation was inapplicable and/or unsafe for achieving hemostasis. Recurrent laryngeal nerves and parathyroid glands were always identified. At the end of the surgery, a single small size (10 Ch) suction drainage tube was applied to the thyroid cavity. Suction drainage or other type of drainage like Penrose drain are not routinely used in conventional thyroid surgery. In this study

TABLE I - Patient baseline characteristics.

	A: Standard treatment (n=65) (n=146)	B: Cellulose gauze (n=60)	C: CFTP
Gender (M/F)	14/51	13/47	21/128
Mean age (years)	51.75	53.1	50.73
Mean $\pm$ SD thyroid volume	42.12 $\pm$ 13.73	41.60 $\pm$ 13.09	42.89 $\pm$ 12.99
Multinodular goiter (n)	53	49	119
Multinodular toxic goiter (n)	5	4	9
Graves disease (n)	7	7	16
Plummer's disease (n)	0	0	2

it was in PVC material and used to evaluate the overall amount of blood and serum loss after the procedure, and to assess the actual difference between the groups. This was removed after 24 hours, and the quantity and quality of the drained fluid was evaluated. Variables analyzed were the drainage volume during the first 24 hours after surgery, and the occurrence of post-operative complications (hematoma, seroma and surgical site infection). Statistical analysis was performed with SAS software, version 9.2. Rates of hematoma, seroma, and surgical site infection were analyzed with a logistic regression model. If the test between groups was statistically significant ( $p < 0.05$ ), multiple paired comparisons were done. The difference in drainage volume was measured by analysis of variance (ANOVA).

## Results

A summary of our results is reported in Table II. Drainage volume up to 24 hours after surgery was significantly reduced with both CFTP and cellulose gauze compared with standard treatment ( $p < 0.001$  for both). In addition, mean drainage volume in the CFTP group was significantly less than in the cellulose gauze group ( $p < 0.001$ ) (Fig. 1). Seroma, appearing usually 3-5 days after surgery, was also significantly different between groups ( $p = 0.003$ ). Seroma was significantly less frequent in the CFTP group compared with either standard treatment ( $p = 0.017$ ) or cellulose gauze ( $p = 0.006$ ). The difference in occurrence of seroma in group B vs group A was not statistically significant. No significant differences between the groups were observed for the occurrence of compressive hematoma, which occurred in only one patient who was undergone immediate surgical reoperation with quickly hemostats control, or surgical site infection, which was observed in a single patient in both the standard care and cellulose gauze groups. All patients underwent clinical and ultrasonographic control after 2-4 weeks with the aim to obtain a more homogeneous groups and verify the complete absorption of the patch and/or the presence of collections into the surgical site.

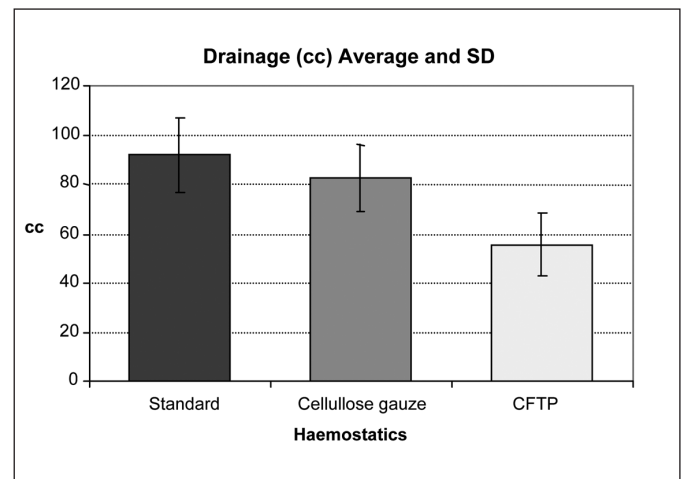


Fig. 1: mean  $\pm$  Standard Deviation (SD) drainage volume (up to 24 hours post-surgery) in post-thyroidectomy patients.

## Discussion

Hemorrhage is an uncommon, but serious, complication of thyroidectomy that can result in life-threatening airway obstruction through impaired venous and lymphatic drainage, leading to laryngopharyngeal edema<sup>3</sup>. Hemorrhagic symptoms include the sensation of neck pressure or pain, dysphagia, dyspnea, stridor, and respiratory distress. These symptoms typically occur early in the post-operative period, often within 6 hours after surgery<sup>6,7</sup>. In one large-scale retrospective review, the time from thyroidectomy to symptom onset was less than 6 hours in 43% of cases, between 7 and 24 hours in 38%, and beyond 24 hours in 19% of cases<sup>8</sup>. If symptoms appear, immediate intubation and surgical re-exploration are needed in order to avoid complete airway obstruction<sup>6</sup>. The origin of hemorrhage can be the opening of a previously coagulated vessel, slipping of a ligation, or bleeding from residual thyroid tissue. However, in some cases it is impossible to determine the source of bleeding, and surgical re-exploration does not show

TABLE II - Occurrence of hematoma: seroma and surgical site infection and drainage volume in post-thyroidectomy patients

	Hematoma n (%)	Seroma n (%)	Surgical site infection n (%)	Drainage (ml)* Mean $\pm$ SD
A: Standard treatment (n=65)	1 (1.5)	6 (9.2)	1 (1.5)	92.11 $\pm$ 15.32
B: Cellulose gauze (n=60)	0 (0.0)	7 (11.7)	1 (1.7)	82.58 $\pm$ 13.61
C: CFTP (n=146)	0 (0.0)	2 (1.4)	0 (0.0)	55.68 $\pm$ 12.77
Differences between groups:	p=0.238	p=0.003	p=0.211	p<0.001
Standard treatment vs. cellulose gauze		p=0.656		p<0.001
Standard treatment vs. CFTP		p=0.017		p<0.001
Cellulose gauze vs. CFTP		p=0.006		p<0.001

\*Drainage up to 24 hours post-surgery.

any hemorrhagic cause after the hematoma has been drained<sup>2,3,6-8</sup>). Risk factors for post-operative bleeding, apart from a defined coagulopathy, are not well known. Several studies have evaluated factors often associated with post-thyroidectomy cervical hematoma, such as hyperthyroidism, especially that associated with Graves disease<sup>2,7,9-12</sup>, extent of surgery<sup>8,13</sup>, re-operations<sup>14</sup>, malignancy<sup>8,15-16</sup>, and large and/or sub-sternal goiters<sup>12,17</sup>, but results are contradictory and often not statistically significant. Aspects of surgical technique, such as not sectioning the pre-thyroid muscles, or the use of minimally invasive or endoscopic techniques<sup>3,18-19</sup>, can reduce the risk of hemorrhage. The use of such instruments as the harmonic scalpel, and radiofrequency or thermal devices, also improves vessel sealing<sup>20</sup> though further randomized studies are needed to assess their capacity to prevent major hemorrhagic complications in thyroid surgery<sup>3</sup>. The ability of suction drainage to reduce the incidence of post-thyroidectomy hemorrhage is a debated topic. As hemorrhagic complications are rare, but feared, the insertion of one or two drains is a generally accepted procedure. However, recent studies have suggested that suction drainage does not detect bleeding or prevent respiratory distress, and can sometimes lead to hemorrhage<sup>21-22</sup>. Moreover, use of drains can lengthen post-operative hospital stay, increase the risk of surgical site infection, and delay the patient's return to normal activities<sup>21</sup>. The first step in preventing hemorrhagic complications is meticulous hemostasis during surgical procedures. In addition, several topical products are available to help the surgeon achieve hemostasis, though there is only limited evidence that these tools help prevent post-thyroidectomy hemorrhaging. Products we use in our center include oxidized cellulose gauze and CFTP, both of which are widely used. The haemostatic mechanism of bio-absorbable oxidized cellulose gauze is not well known, though it is believed that the cellulose gauze forms a coagulum of cellulosic acid salts that link hemoglobins, resulting in clot formation after contact with bleeding tissue<sup>23</sup>. The clot is then degraded and absorbed within a maximum period of 7 days. Oxidized cellulose gauze is deemed to have a bacteriostatic effect<sup>24</sup>, but the possibility of a foreign body reaction<sup>25</sup>, though limited, could have undesirable effects, such as an increase in the incidence of seroma, as observed in this study. CFTP is a collagen sponge coated on one side with human fibrinogen and thrombin, the use of which results in tissue adhesion and sealing. It is activated by moisture on application, and requires less than 4 minutes to exert its effect; it is enzymatically degraded and safely absorbed by the body within 12 weeks of application<sup>26</sup>. CFTP is indicated in adults for supportive treatment in surgery for improvement of hemostasis, promotion of tissue sealing, and for suture support in vascular surgery in which standard techniques are insufficient. In addition, it is widely used in abdominal (open and laparoscopic) and thoracic surgery. The use of

absorbable topical haemostatic agents has been assessed in several studies across different surgical fields<sup>27-30</sup>. These tools are generally accepted as an improvement in hemostasis of the thyroid bed after a thyroidectomy<sup>3,31-32</sup>, but their real efficacy is uncertain, and their use is principally based on a cautious approach towards hemorrhagic control rather than robust data showing real advantages. In this study, no hemorrhagic complications occurred in patients treated with cellulose gauze or CFTP. However, one hematoma was observed in the standard care group, in a patient who received no topical haemostatic agent. The limited occurrence of hemorrhagic events suggests that it is not possible to confirm the capacity of topical haemostatic agents to prevent this complication. Our results show a significant reduction in drainage volume with both CFTP and oxidized cellulose gauze. This could indicate a capacity to prevent or reduce the incidence of bleeding in thyroid surgery. In addition, we also observed other advantages in the CFTP group, namely a significant reduction in seroma and no local surgical site infection. Postoperative seroma may result from thyroid surgery. It is generally considered a minor complication, but it needs a clinical follow-up. Large seromas need aspiration under sterile conditions and repeated aspirations may be necessary. This complication can be contaminated by pathogens that could be present on the skin and can lead to surgical site infection. Seroma occurs in 2 to 7% of thyroidectomies<sup>1</sup>. It may lead to readmission, re-intervention, antibiotic therapy, repeated medications, which correlate with increased morbidity and costs<sup>33</sup>. Surgical site infection after thyroid surgery generally occurs in 0.9% - 3.2% of patients. This may be related to pre- and intra-operative antiseptic precautions and procedures, as well as not well-known local and systemic factors<sup>1,34-37</sup>. In the cellulose gauze group, the incidence of seroma was significantly higher than in the CFTP group. The occurrence of surgical site infection that we observed in the cellulose gauze group, and in the non-haemostatic group, appeared to be sporadic, and not statistically significant. Despite these results, we estimate that the increase in the amount of drainage fluid and, in particular, the occurrence of seroma may constitute a predisposition to septic complications. However, foreign-body reactions have been described elsewhere after cellulose gauze application<sup>38</sup>. Though this study involved a large series of patients for more than two years, larger series of patients evaluated in longer observation periods, and/or in multicentric studies, and in randomized trials are needed to assess the efficacy of haemostatic agents in reducing the incidence of compressive hematoma after thyroid surgery. In our study, both haemostatic agents provided a significant reduction of drainage fluid in the first 24 hours after surgery, suggesting they are effective in improving surgical haemostasis. Of the two agents evaluated, CFTP showed clear advantages over cellulose gauze in reducing drainage volume and seroma, which led us to use this agent more extensively.

## Conclusions

According to our experience, the use of CFTP as haemostatic agent may improve the comfort of patients' post-operative hospital stay, as well as reduce their length of stay, and allow for more rapid resumption of normal daily activities. In this sense, improved quality of surgery leads directly to an improved quality of patients' lives. Moreover, this may facilitate the option of one-day surgery, with attendant quality-of-life improvements, and cost-benefits, for health care systems. Moreover, a more great casuistry is need to certificate real and effective reduction of hemorrhagic complication.

## Riassunto

Un obiettivo fondamentale in chirurgia tiroidea è l'ottenimento di un'emostasi efficace per ridurre il rischio di complicanze potenzialmente pericolose per la vita del paziente, come l'ematoma compressivo. Scopo del nostro lavoro è valutare l'efficacia di due agenti emostatici locali ampiamente utilizzati: una garza di cellulosa ossidata rigenerata e un patch di collagene-fibrinogeno e trombina (CFTP) in pazienti sottoposti a tiroidectomia totale. Il nostro è uno studio prospettico, comparativo, non randomizzato in cui pazienti sottoposti a tiroidectomia totale per patologia benigna hanno ricevuto un trattamento chirurgico tradizionale, senza l'utilizzo di alcun agente emostatico, garza di cellulosa o CFTP. I paramenti principalmente utilizzati sono stati il volume del drenaggio nelle 24 ore dopo trattamento chirurgico e la comparsa di eventuali complicanze post-operatorie (ematoma, sieroma, infezione del sito chirurgico). Abbiamo arruolato 271 pazienti, di cui 65 hanno ricevuto un trattamento chirurgico standard, 60 sono stati operati con l'ausilio della garza di cellulosa, e su 146 pazienti abbiamo applicato il CFTP. La comparsa di sieroma è stata significativamente inferiore nel gruppo in cui era stato utilizzato il CFTP confrontato sia con il gruppo che aveva ricevuto la garza di cellulosa ( $p=0.006$ ) sia con il gruppo sottoposto a trattamento chirurgico tradizionale ( $p=0.017$ ). Un'evidente riduzione del volume del drenaggio è stato inoltre osservato nel gruppo con CFTP confrontato con gli altri due gruppi ( $p<0.001$ ). Il volume del drenaggio si è ridotto in modo significativo anche nel gruppo della garza di cellulosa rispetto al trattamento tradizionale ( $p<0.001$ ). Nessun evento settico è stato osservato dopo l'applicazione del CFTP. Si è verificato un solo caso di ematoma nel gruppo in cui non è stato utilizzato alcun emostatico. Entrambi gli agenti emostatici utilizzati hanno determinato una riduzione della quota di materiale siero-ematico nelle immediate 24 ore post-operatorie; nello specifico, il CFTP si è dimostrato più efficace rispetto alla garza di cellulosa. L'uso degli agenti emostatici può incrementare la

qualità della chirurgia tiroidea, migliorando il confort post-operatorio e riducendo la durata della degenza ospedaliera.

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