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Original Article

Artiss® and burn treatment: a retrospective analysis contributing to current clinical practice

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Abstract: Background: Tangential excision and autologous skin graft coverage is a foundational principle in burn surgery. Fibrin sealant (Artiss®) was developed recently as alternative to staples for graft fixation. The aim of this study was to assess whether graft-fixation with Artiss shows profit in terms of postoperative pain management compared to graft fixation with staples. Methods: A retrospective single-center, single-surgeon frequency-matched cohort study was completed on 83 patients with thermal injury burns covering 1%-25% of total body surface area, requiring early excision and immediate coverage with split-thickness skin grafts. Grafts were fixated with Artiss only or staples only. Primary outcome parameters include complication rates (graft loss, need for regrafting and wound contamination), the requirement of pain medication for postoperative pain and the need for narcosis for postoperative procedures. Results: Graft-fixation with Artiss resulted in a decrease in administration of analgesics *(P=0.005)* and anesthetics *(P=0.007)* postoperatively. No statistically significant difference was found in complication rates *(P=0.999)* between both groups. Conclusion: Fibrin sealant proved to be a safe and effective alternative to staples for graft fixation. It showed profit in short-term burn outcomes, reducing the need for analgesics and anesthetics postoperatively.

Keywords: Artiss, slow-clotting fibrin sealant, staples, autologous skin graft, burn treatment

Introduction

Topical treatment has been the golden standard for burn management for many centuries [1, 2]. It was not until the 20th century that things started to change when Janzekovic introduced the concept of tangential excision and immediate skin grafting for full-thickness and deep partial-thickness burns as a new standard of care [3].

Over the years, mortality and morbidity in burn surgery have improved significantly. Nevertheless, besides burn resuscitation and fluid replacement, the concept of tangential excision and immediate coverage remains rule number one in the approach of a burn patient. In terms of covering the excised wounds, autologous split-thickness skin grafts have evolved as being optimal for full-thickness dermal defect coverage. In order to fixate these grafts, sutures and staples represent the standard method of fixation. Over the last decades however, the use of fibrin sealant has gained popularity as graft fixation method because of the well-known haemostatic and adhesive properties [4-7]. The single product available in this category (Artiss®, Baxter, Westlake Village, CA) is considered a recent and refreshing evolution within burn surgery. Artiss is a slow-clotting fibrin sealant and consists of two plasma-derived components: a sealer protein solution and a thrombin solution. The sealer protein solution contains human fibrinogen 91 mg/mL, synthetic aprotinin 3000 KIU/mL and a fraction of human factor XIII. Human thrombin 4 IU/mL and calcium chloride 40 µmol/mL are components of the thrombin solution. Both compounds are provided frozen in two preloaded syringes presented in a single spraying device ready for topical application after thawing. Even though this product has been approved by the U.S. Food and Drug Administration (FDA) in 2008, clear clinical evidence on the use of this product is minimal.

The aim of this study was to assess whether the use of Artiss for graft fixation shows profit in terms of postoperative pain management compared to graft fixation with staples.

Methods

Study design

We performed a single-centre, single-surgeon, retrospective frequency-matched cohort study on 83 burn victims treated in the University Hospitals Leuven. Inclusion criteria for this study were thermal injury burns covering 1%-25% of total body surface area (TBSA) requiring early excision and immediate coverage with split-thickness skin grafts. Exclusion criteria were non-thermal burns (friction, electrical and chemical burns), graft fixation with skin glue or a combination of staples and fibrin sealant as well as severe comorbidities leading to impaired wound healing such as nicotine addiction, diabetes and morbid obesity. Burns extending >25% of TBSA were excluded because of possible bias on pain measurement when compared to smaller burns. All patients operated within a predefined one-year timeframe that met inclusion criteria were selected for further analysis. We created a study cohort consisting of 42 consecutive patients treated with Artiss in 2014, the first year that this fibrin sealant was used regularly for graft fixation. We used a comparative cohort of 41 patients, including all patients who met the inclusion criteria and who were treated with staples in 2007, the last year in which all grafts were fixated with staples. In the time between, grafts were fixated with skin glue, a former type of fibrin sealant or combined fixation methods. Both cohorts were frequency-matched for sex, age, TBSA and location of the burn. Outcome parameters investigated were complication rates and the requirement of analgesics and anesthetics postoperatively.

Operating technique and postoperative care

Preparation of the wound occurred in the same way in all patients. The wound bed was debrided under general anesthesia until a well-bleeding surface appeared. Eschar was removed with a hand dermatome and the wound bed was denuded by hydrosurgery (Versajet® Hydrosurgery System, Smith & Nephew, London, UK). Oozing of blood was reduced by means of manual pressure. The most important bleeding spots were coagulated. Skin grafts were taken split-thickness (0.008 inch) by air dermatome (Zimmer® Air Dermatome, Zimmer Biomet, Warsaw, IN). Donor sites included thighs and lower abdomen. Paraffin was administered before graft prelevation. When meshing was indicated, a hand-driven meshing device (Zimmer® Skin Graft Mesher, Zimmer Biomet, Warsaw, IN) was used. Next, the graft was measured and positioned on the wound bed. After thawing, Artiss was administered topically by spraying the product from side to side in a thin layer that covers the whole wound. A distance of 20 centimeters between spraying device and wound bed was used. The recommended dosage is 2 mL to cover 100 cm^2. However, our results were obtained by using an ultra-thin layer of 2 mL for approximately 400 cm^2. In contrast with previous forms of fibrin sealant, the low thrombin concentration of Artiss allows for graft manipulation up to 60 seconds [8]. In the control group, staples were circumferentially placed on regular intervals (7-10 mm), attaching the graft to healthy surrounding tissue by means of a disposable skin stapler (Precise Vista® skin stapler, 3 M, Saint Paul, MN). The same type of dressing was used in both study populations. The recipient sites were covered with Surfa-Soft® (Taureon, Rijswijk, NL), antiseptic gel (Iso-Betadine® gel, Meda Pharma, Brussels, BE), a non-adherent dressing (Jelonet® Paraffine Gauze Dressing, Smith & Nephew, Victoria, AU), large compresses and loosely applied bandages. Patients were transferred to the burn care unit for further observation and specialized wound care. A uniform, preformulated and standardized pain protocol was applied postoperatively for both treatment groups. After a starting dose, background pain was treated with Piritramide (Dipidolor®) IV on a continuous rate of 2-4 mg/h for adults and 0.03-0.06 mg/kg/h for children. A bolus of Piritramide was administered for breakthrough pain. Procedural pain was prevented by administration of one bolus of Sufentanil (Sufenta®) IV 0.5-1 μg/kg at least 5 minutes before the procedure. When pain was not controlled sufficiently, anesthetics were used. After discharge from the hospital, patients were seen in the outpatient clinic 4 weeks after discharge and subsequently on a three-monthly

Table 1. Comparison of gender, age, total body surface area (TBSA) and location of the burn in patients treated with staples vs. Artiss

	Staples	Artiss	*P*-value
N=83	41	42	
Gender, n (%)			*0.573*
Male	17 (42)	20 (48)	
Female	24 (58)	22 (52)	
Age			*0.521*
Mean	45	41	
Median	44	47	
Range	1-87	1-88	
TBSA			*0.955*
Mean	5.1	4.9	
Median	2	3	
Range	1-25	1-23	
Location, n (%)			
Face/Scalp	2 (5)	3 (7)	*0.999*
Abdomen/Thorax	7 (17)	8 (19)	*0.815*
Arm	14 (34)	14 (33)	*0.938*
Hand	5 (12)	1 (24)	*0.109*
Leg	9 (21)	9 (21)	*0.954*
Foot	4 (10)	7 (17)	*0.353*

basis to assess scar tissue and adjust scar therapy. When scar outcomes were considered to be satisfactory, no more follow-up appointments were made.

Outcome parameters

All outcome parameters were assessed during hospitalization. Relevant complications were defined as total graft loss, need for regrafting for total or partial graft loss and infection. We defined 'total graft loss' as loss of >75% of applied graft tissue due to non-take of the graft on the wound bed. When an inferior secondary healing response was expected in case of total or partial graft loss, i.e. based on size or location of the wound, regrafting was performed. Wound infection was defined as wound swabs showing positive wound cultures. Wound swabs were taken based on clinical features (smell, fluid secretion, poor wound healing,...). Postoperative pain was assessed by the administration of extra analgesics on top of the preformulated pain protocol for breakthrough pain and by the requirement of anesthetics postoperatively for procedural pain, representing pain during physiotherapeutic manipulations or during dressing changes.

Statistical analysis

Frequency-matching for both cohorts was performed according to gender, age, TBSA and location of the burn. These parameters were assessed for every patient and differences between the study cohort and comparison cohort were tested by using chi-square test and *t* test. A binominal logistic regression was performed to ascertain the effects of the graft-fixation method on the likelihood that patients would require extra analgesics or anesthetics postoperatively. We hereby included the effect of five covariates on this likelihood: gender (male vs. female), age, TBSA, meshing (sheet vs. meshed grafts) and location of the burn. Linearity of the continuous variables with respect to the logic of the dependent variable was assessed via the Box-Tidwell procedure. A Bonferroni correction was applied and all continuous independent variables were found to be linearly related to the logic of the dependent variable. Statistical analysis was performed using IBM SPSS Statistics 23 and significance was defined as $P<0.05$.

Results

We analyzed data of patients treated in 2007 and in 2014. Mean follow-up for the staples group was 9 months (range 1-20 months). Mean follow-up for the Artiss group was 8 months (range 2-15 months). Frequency-matching between both cohorts revealed no statistical significant differences in mean age (*P=0.521*), gender (*P=0.573*), location of the burn (*P>0.05*) and TBSA (*P=0.955*) (**Table 1**).

The decision whether to mesh or not was made by the same surgeon for all grafts. As a rule, full sheet grafts were used in burns ≤1% in visible areas. Other areas were covered with meshed grafts. Full-sheet grafts fixated with staples were used on hands (*n=1*), upper thorax (*n=2*) and face (*n=1*). Sheet grafts in the Artiss cohort were used on hands (*n=1*), upper thorax (*n=3*), face (*n=3*), arms (*n=9*), legs (*n=2*) and feet (*n=4*).

Complication rate

Graft loss of >75% of graft surface occurred in two patients (5%) in the staples group and in one patient (2%) in the Artiss group (*P=0.999*).

Table 2. Complication rates in patients treated with staples vs. patients treated with Artiss

	Staples	Artiss	*P*-value
N=83	41	42	
Graft Loss, n (%)			*0.999*
Loss	2 (5)	1 (2)	
No loss	39 (95)	41 (98)	
Regrafting, n (%)			*0.999*
Regrafting	4 (10)	3 (7)	
No regrafting	37 (90)	39 (93)	
Contamination rate, n (%)			*0.999*
Wound swabs taken	11 (27)	28 (67)	
Positive wound culture	8 (73)	21 (75)	
Negative wound culture	3 (27)	7 (25)	

Regrafting was required for 4 patients (10%) treated with staples and 3 patients (7%) treated with Artiss (*P=0.999*). In the staples cohort, 11 wound swabs were taken and 8 of them showed positive wound cultures (73%). In the Artiss cohort, 21 positive wound cultures were found out of 28 wound swabs (75%). No statistical significant difference was found for incidence of contamination rates between both treatment groups (*P=0.999*) (**Table 2**).

Analgesics

All patients were treated by the same pain protocol postoperatively. Twenty-six patients (63%) out of the staples cohort required extra analgesics on top of the standard pain protocol compared to ten patients (24%) in the Artiss group (**Figure 1**). The logistic regression model was statistically significant, χ^2 (10)= 25.326, *P=0.005*. Sensitivity was 69.4%, specificity was 78.3%, positive predictive value was 71.4% and negative predictive value was 76.6%. Of the six predictive variables, only two were statistically significant: fixation type and TBSA. Patients treated with staples had 5.5 times higher odds to require extra analgesics compared to patients treated with Artiss (*P= 0.005*). Increasing TBSA was associated with an increased likelihood of requiring extra pain medication (*P=0.032*) (**Table 3**).

Anesthetics

Eighteen patients (44%) treated with staples required anesthetics during postoperative procedures, compared to six patients (14%) treated with Artiss (**Figure 1**). Statistically significant results were obtained for the regression model, χ^2 (10)=34.744, P<0.0005. Sensitivity was 58.3%, specificity was 94.8%, positive predictive value was 82.3% and negative predictive value was 84.6%. Of all predictor variables, three were significant. The odds of requiring anesthetics postoperatively were 22 times higher for patients treated with staples compared to patients treated with Artiss (*P= 0.003*), increasing TBSA was associated with higher odds of requiring anesthetics (*P=0.011*) whereas increasing age was associated with lower odds of requiring anesthetics for postoperative procedures (*P=0.007*) (**Table 4**).

Discussion

The comparison of graft fixation with staples and slow-clotting fibrin sealant (Artiss) in humans has been investigated in a phase 1/2 and phase 3 clinical study, performed in 2007 and in 2008 respectively [9, 10]. All patients were treated with either fibrin sealant or staples at two comparable test sites. Similar long-term outcomes in terms of scar appearance were described, providing satisfactory results compared to conventional techniques. They concluded that fibrin sealant is a safe fixation method, which seems to be at least as effective as staples. In this report, we could confirm that using Artiss was safe and effective to fixate grafts to the wound bed in burns. Complications assessed included graft loss, need for regrafting and contamination rates. Our results indicated equal complication ratios between the two treatment groups (P=0.999). We did notice a higher amount of wound swabs taken in the Artiss group (67% vs. 27%). Several causes might explain this finding. Since wound swabs were taken based on clinical features, we could assume that Artiss-fixated grafts showed more clinical findings suggesting infection. However, similar contamination rates were found between both groups. On the other hand, higher vigilance and faster screening could explain the frequency of taking wound swabs as well.

Burn wounds are often painful, disabling and therefore psychologically challenging injuries. Burn victims are shown to have more pain during manipulation than at rest. The most painful procedures are reported to be dressing chang-

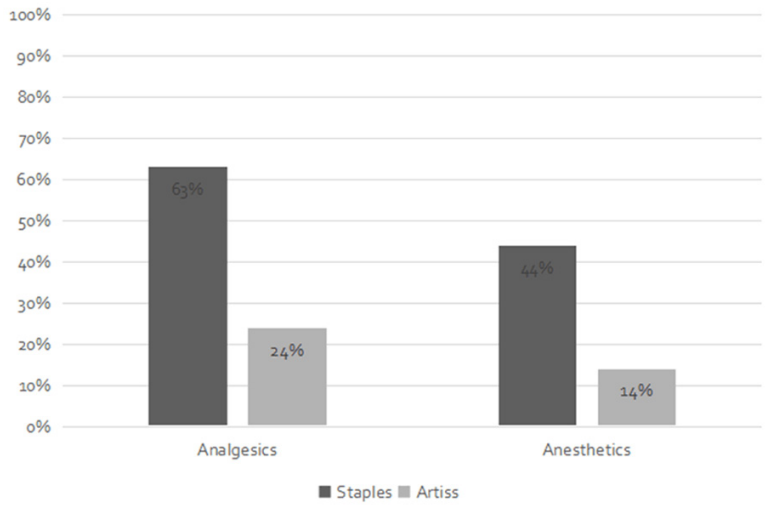

Figure 1. Requirement of analgesics and anesthetics for the staples cohort and Artiss cohort.

Table 3. Logistic regression predicting likelihood of requiring analgesics based on age, gender, meshed grafts, location and fixation method

	Significance	Odds Ratio	95% Confidence Interval for Odds Ratio	
			Lower	Upper
TBSA	*0.032*	*1.161*	*1.013*	*1.330*
Age	*0.564*	*0.994*	*0.973*	*1.015*
Gender	*0.373*	*1.634*	*0.555*	*4.806*
Meshed	*0.259*	*0.451*	*0.113*	*1.795*
Location	*0.894*			
Fixation	*0.005*	*0.181*	*0.055*	*0.598*

Note: gender is for males compared to females, meshing is for sheet grafts compared to meshed grafts and fixation is for Artiss compared to staples.

Table 4. Logistic regression predicting likelihood of requiring anesthetics based on age, gender, meshed grafts, location and fixation method

	Significance	Odds Ratio	95% Confidence Interval for Odds Ratio	
			Lower	Upper
TBSA	*0.011*	*1.237*	*1.050*	*1.458*
Age	*0.007*	*0.961*	*0.934*	*0.989*
Gender	*0.402*	*1.758*	*0.470*	*6.579*
Meshing	*0.066*	*6.546*	*0.882*	*48.583*
Location	*0.733*			
Fixation	*0.003*	*0.044*	*0.006*	*0.341*

Note: gender is for males compared to females, meshing is for sheet grafts compared to meshed grafts and fixation is for Artiss compared to staples.

es [11]. We investigated postoperative pain management by analyzing the requirement of extra pain medication for breakthrough pain and narcosis for pain during manipulations postoperatively (i.e. dressing changes or physiotherapy). Our results showed statistically significant differences between both treatment groups. The use of fibrin sealant resulted in a reduced need for pain medication as well as a decreased use of narcosis postoperatively. This finding could be explained by an additional pain-response of tissues to stapling. Staples are foreign bodies, inducing local tissue inflammation and pain. Fibrin sealants are biological products consisting of components similar to the patient's own tissues. Indeed, the ultrastructure of fibrin sealant clots resembles the structure of natural blood clots. Therefore, they do not induce a reactional process with additional inflammation and pain. On the contrary, they even seem to lower inflammation rates [12]. *In vitro* results show that fibrin sealant clots promote adhesion and migration of endothelial cells, fibroblasts and keratinocytes, improving neovascularization, formation of an extracellular matrix and skin healing respectively [13, 14]. Consequently, the use of fibrin sealant may not only lead to less pain and lower inflammation rates in the initial phase of wound healing, but also to enhanced soft tissue regeneration and therefore even faster wound healing times. On the long term, this may implicate less scar contraction, less redness and less scar hypertrophy, contributing to better outcomes in burn surgery [15, 16]. Yet, long-term effects of fibrin sealant on scar maturation are still to be investigated.

The use of full sheet grafts also contributes to better burn scar outcomes. Full sheet grafts are preferably used in visible areas since sheet grafts show better results both functionally and aesthetically [15, 17, 18]. Our results showed that fewer grafts were meshed in the Artiss group. In this study, the choice whether to mesh or not was purely based on the sur-

geon's decision. Yet, we noticed a shift in the use of full sheet grafts: in the staples group, sheet grafts were used in visible areas (face, upper thorax and hands). In the Artiss cohort, application of full sheet grafts was extended to less visible areas such as feet, legs and arms. We hypothesize that fibrin sealant, which is applied over the entire wound, promotes a larger contact area between the graft and wound bed compared to point fixation obtained by staples. This implies that less space remains for hematoma and seroma formation. This could thus contribute to higher rates of full-sheet graft-take. Nonetheless, this hypothesis should be confirmed in a randomized prospective trial comparing meshed and full-sheet grafts.

The use of fibrin sealant however, does come at a cost. The price of Artiss (116 €/2 mL) is substantially higher than the price of staples (13 €/35 staples). Nevertheless, the beneficial cost-benefit ratio of using fibrin sealant as graft-fixation method has been reported before [19]. A reduction in need for analgesics or anesthetics importantly lowers costs. In addition, staples have to be removed after several days. To many patients, this is an uncomfortable event, which causes distress, fear and necessitates extra pain medication [10, 11]. Indeed, this procedure does require time, paramedic staff and money, which can be eliminated with the use of fibrin sealant [19].

This report has several limitations. First of all, due to the retrospective nature of this study, we could not implement randomization or a predefined follow-up period. These data were influenced by intra-operative decision-making by the surgeon (selection bias). The selection of staples or fibrin sealant and meshed or full-sheet grafts was based on clinical judgement. Additionally, we defined the time to complete cure as the number of follow-up visits, which could have created bias. Moreover, we could only use recorded data. Subsequently, no objective or subjective scar assessment could be implemented. Yet, we believe that these data show substantial evidence of the beneficial effects of fibrin sealant on postoperative pain in the treatment of burn wounds.

Conclusion

To conclude, even though the crucial role of fibrin in wound healing has been explored and implemented by surgeons for over a century [20-23], the emerging use of fibrin sealant in burn surgery as alternative to staples for graft fixation is a relatively recent phenomenon [9, 10, 24]. Artiss is a slow-clotting fibrin sealant, approved by the FDA in 2008. It is the only product available up to now for this purpose. This product proves to be a safe and effective alternative to staples for graft fixation. The use of fibrin sealant allowed for a significant reduction in pain and discomfort in the postoperative phase compared to the use of staples. Additionally, extended application of full sheet grafts to less visible areas might improve functional and aesthetical results. Further research with a long follow-up period is required to contribute to this hypothesis. Nevertheless, the results of this study indicate a valuable role for the use of fibrin sealant in burn surgery.

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Disclosure of conflict of interest

None.

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