Montrouge, le 01/11/2012

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paru dans
European Journal of Dermatology, 2011, Volume 21, Numéro 6

John Libbey Eurotext

Eur J Dermatol 2011; 21(6): 895-8

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Article accepted on 8/18/2011

Smoking and diabetes mellitus type 2 reduce skin graft take; the use of fibrin glue might restore graft take to optimal levels

Efficacy has been demonstrated in some uses of fibrin glue associated with graft loss. Smoking and hyperglycemia significantly decrease the success of skin graft survival in specific injuries. This retrospective study aimed to verify the association with decreased skin graft survival and whether fibrin glue is useful in reversing the influence of these factors. This bicentric, retrospective, cross sectional case control study was carried out on 1881 medical patients. Patients who met inclusion criteria were admitted to the Plastic Surgery Service of Reina Sofia University Hospital (Spain) and the Trauma/Burn intensive Care Unit of UAB Hospital at Birmingham (USA) between January 2000 and December 2009. The successful graft take for each group and its control were analyzed by a Chi-square test; the confidence interval was 95%. Smoking and DM type 2 decrease skin graft survival when compared with their control groups. There was a statistically significant improvement in skin graft take when fibrin glue was used. The percentage improvement in the control groups was approximately 10%, whereas in the study groups it was 2-3 times higher. We conclude that graft loss is associated with smoking and DM type 2, but fibrin glue might restore graft adherence to almost normal levels.

Key words: affixing skin grafts, graft fixation, graft loss, graft survival, hyperglycemia

Fibrin glue has many potential applications in plastic surgery; these applications are commonly associated with seroma and hematoma prevention, face lifting, microvascular anastomosis and skin grafting. Efficacy of its use is difficult to establish based on the lack of adequately powered prospective trials [1]. Nevertheless, its efficacy as a haemostatic and sealing agent has been clearly established and the product is licensed in European countries by the EMA (European Medicines Agency) on the basis that it is an effective product when haemostatic or sealing effects are targeted.

The use of fibrin glue for affixing skin grafts is likely the most investigated application for it within plastic surgery. The potential benefits of fibrin glue in affixing skin grafts can be due to three potential properties: hemostasis, greater graft adherence, and antibacterial action [2]. Fibrin glue in skin grafting has gained popularity due to its use in achieving hemostasis and graft fixation [3].

Early skin graft survival depends on stabilization of the graft by the fibrin network between the graft and the recipient bed. Fibrin glue provides an immediate, highly cross-linked fibrin network that will stabilize the graft and facilitate graft nutrition by serum imbibition (plasmatic circulation) with subsequent ingrowth of vascular buds (neovascularization) [2].

In situations associated with poorer graft take, such as infected tissue and difficult anatomical areas complicated by unavoidable movement, fibrin glue has been shown to improve graft take. Vibe and Pless [4] found an improvement in skin graft take from 83% to 92% with the use of fibrin glue. Furthermore, they found that in difficult areas, such as over mobile muscle or close to skin folds, the percentage of improvement was higher - 88% of cases were successful with fibrin glue, compared to 44% successful cases without it.

Vedung and Hedlung [5] demonstrated the efficacy of fibrin glue in skin grafts of contaminated burn wounds, and in areas difficult to immobilize like the axilla, perineum, and gluteal folds.

Smoking [6] and hyperglycemia [7] have only been demonstrated to significantly decrease the success of skin graft survival in two situations, the first one in digital tip amputation and the second one in burns patients. As previously stated, fibrin glue has been shown to improve graft take in areas complicated by infection and unavoidable movement. We hypothesized that fibrin glue could also improve graft take in patients who smoke, and in diabetic patients. The aim of this retrospective study was two-fold: to determine if smoking and diabetes mellitus type 2 are factors associated with lower skin graft survival when the etiology of the injury is multifactorial. Secondly, if the previous statement was true, to investigate whether there was a significant percentage of improvement in this patient population when fibrin glue was used for affixing skin grafts.

doi:10.1684/ejd.2011.1532

To cite this article: Pérez-Guisado J, Gaston KL, Benítez-Goma JR, Cabrera-Sánchez E, Fidalgo-Rodríguez FT, Rioja LF, Thomas SJ. Smoking and diabetes mellitus type 2 reduce skin graft take; the use of fibrin glue might restore graft take to optimal levels. *Eur J Dermatol* 2011; 21(6): 895-8 doi:10.1684/ejd.2011.1532

Material and methods

Subject selection

This was a bicentric, retrospective, cross sectional case control study. For the Spanish arm of the study, authorization by an ethics committee of the University Hospital of Reina Sofia (Córdoba, Spain) was unnecessary as the study fulfilled the requirements to be excluded from this obligation. These requirements included the privacy and confidentiality of the patients, no contact made with patients during or after completion of study, all data to be stored on password-protected institutional computer from our systems and no monetary compensation related to the research or ownership interest. For the American arm of the study we applied for and received the authorization of the institutional review board (IRB) of UAB (protocol number: X100615005). Patient anonymity was preserved in both arms of the study.

1881 patients (1124 from Birmingham and 757 from Cordoba) were treated with skin grafts from the Plastic and Reconstructive Service at the University Hospital of Reina Sofia and from the Trauma/Burn intensive care unit of UAB Hospital at Birmingham, from January 2000 to December 2009. The inclusion criteria selected for our study were as follows: any injury requiring skin grafts, skin grafted with staples, clinical charts with a complete report on the location and percentage of total body surface area (TBSA) for each grafted area and skin graft survival area, grafted patients with less than 20% TBSA, and age >18 years. In order to minimize potential confounding effects, we excluded patients who were simultaneously smokers and type 2 diabetics, as well as the following: alcoholic habits, immunodepressive states, poor nutritional status, wound bed infections, and wounds located in the axilla, perineum and gluteal folds. The patient sample was representative of all smokers and type 2 diabetics patients hospitalised in the cited burn units.

The chart review was performed by a trained plastic surgeon with long standing experience in chart reviews.

The clinical criteria for undergoing a graft with or without fibrin glue was based on just the physician's subjective criteria. This was due to the lack of consensus among physicians concerning the use of fibrin glue in both arms of the study. In fact, most of them had opposed criteria. On the one hand, there were physicians who use fibrin glue for all patients because they thought that all of them could benefit from fibrin use. Whereas, on the other hand, there were physicians who never used fibrin glue because they thought fibrin use for skin graft take is not worthwhile. There were also physicians who used fibrin glue just when they thought it was necessary, depending on the location of the injury. For that reason, the decision was based on haphazard and subjective criteria. This lack of cohesive criteria encouraged us to design this study and favoured the approval by the IRB.

We considered for this study DM type 2 subjects who were only under insulin therapy and had a diabetes history longer than 10 years. We considered smoking subjects with a consumption higher than 20 cigarettes per day and a smoking history longer than 10 years.The DM type 2 subjects and the smoking subjects were compared respectively to their age-sex-TBSA matched control groups.

When fibrin glue (Tissucol®, Baxter) was used, it was sprayed as a thin layer over the external surface of the wound before the graft took place. The volume used of Tissucol® depended on the wound area affected. The spray set was a disposable kit consisting of a connecting tube with a sterile filter and head for spraying Tissucol® fibrin sealant. Tissucol® Kit composition was as follow: Aprotinin Bovine 1.67 UPE; Coagulation Factor XIII 10 IU; Fibrinogen Human 90 mg; Fibronectin Human 5.5 mg; Plasminogen Human 0.08 mg; Thrombin Human 500 IU.

If a patient had more than one grafted area, we combined the areas in order to simplify the collection of data and the statistical analysis. Successful graft "take" was defined as survival of 70% to 100% of the grafted area as assessed on postoperative day >7.

We considered a maximum TBSA of 20%, as this was the size threshold capable of being treated at the burn unit of the University Hospital of Reina Sofia. We did not include people under 18 years of age since the ethics committee from UAB did not permit it.

Statistical analysis

Our first step was to determine if control groups were equivalent to their respective study groups for the matched variables *(table 1)*. Once this was confirmed, the statistical differences between the percentage of successful graft take for each group and its control were analyzed by a Chi-square test *(table 2)* with SPSS 12.0 (SPSS Inc., Chicago, IL, USA) and are expressed as mean±standard deviation. The confidence interval chosen for statistical differences was 95%.

Results

As shown in table 1, control groups were equivalent to their respective case groups (smokers and type 2 diabetics) for the matched variables: age, sex and TBSA. Approximately 62% of subjects in the smoker/control groups had sustained burn injury, while only 3% of patients belonging to the diabetics/control groups had burn injury.

Table 1. Characteristics of patients.

	Age	Sex: male/female	n	TBSA	Significance level
Smokers	49±12	62%/38%	675	8.1%±3.5	p>0.05
Control	48±14	59%/41%	732	8.3%±4.2	
DM type 2	67±9	54%/46%	221	1.2%±0.3	p>0.05
Control	65±11	53%/47%	253	1.2%±0.4	

Table 2. Percentage of graft take comparing fibrin+staples with staples alone.

	Fibrin+staple graft take	P value[1]	Staple graft take	P value[2]	% Improvement	P value[3]
Smokers	87%±3.7	p>0.05	70%±4.5	*p<0.05	17%	*p<0.05
Control	93%±1.6		85%±1.9		8%	*p<0.05
DM type 2	84%±4.2	p>0.05	58%±5.3	*p<0.05	26%	*p<0.05
Control	88%±2.1		79%±2.7		9%	*p<0.05

P values[1,2] are for comparisons between reference and control groups. P value[3] is for comparison inside each group (Fibrin+staple graft take vs Staple graft take alone).

As there were no significant differences in both arms of the study for all the parameters examined (p>0.05), the data of both arms were pooled and presented together.

As shown in *table 2*, there is a statistically significant improvement in skin graft take in all the groups, including the control groups, when fibrin glue was used. Comparing stapled graft take in smokers and subjects with DM type 2 with their respective control groups, we can appreciate that smoking and diabetes decrease the percentage of success of skin graft survival. Furthermore, the effect of diabetes is stronger than the effect of smoking. A decrease in graft take of 15% was seen in the smoking subjects (from 85% to 70%), and a decrease of 21% was seen in subjects in the diabetic group (from 79% to 58%).

In the control groups, the percentage of improvement when fibrin glue was used was approximately 10% (8% for the smoker control group and 9% for the diabetics control group). However, in the reference groups the percentage of improvement was approximately 2 to 3 times higher in comparison to each control group. In the smokers group, the percentage of improvement was 17% (from 70% to 87%) compared with the 8% improvement for its control group (from 85% to 93%). In the diabetic group, the percentage of improvement was 26% (from 58% to 84%) compared with the 9% improvement for its control group (from 76% to 88%).

When fibrin glue is used we can appreciate that the differences between the reference groups and the control groups are reduced and statistically equal, compared to grafts that are only stapled [6% for the smokers/ control groups (from 93% to 87%), and 4% for the diabetic/control groups (88% to 84%)].

Discussion

Smoking has been demonstrated to significantly decrease the success of skin graft survival in digital tip amputation [6], and hyperglycemia [7] has the same effect in the burn population. We strengthen these findings with our data as both smoking and diabetes mellitus type 2 are factors associated with decreased skin graft survival in all the injuries we studied. Our findings suggest that DM type 2 is associated with greater negative impact on skin graft survival than smoking. When staples alone are used for affixing graft, the diabetic study group had a decreased percentage of graft survival of 21%, whereas the smoking study group decreased its percentage of graft survival by only 15%. Regardless, we should interpret these results carefully since both diabetic case and control groups were almost 20 years older than the subjects in the smoking/control groups. There may be confounding factors associated with old age that we have not analysed which may influence these results. The age difference could also explain why the TBSA was higher for the smoking/control groups compared with the diabetic/control groups (8.2%vs 1.2%) due to the nature of the injury. Burn injuries are more common in 38±18 years old people [8], and the likelihood of requiring skin grafts is greater when a burn is the mechanism of injury. To further support this point, 62% of patients in the smoker/control groups had sustained burn injury, while only 3% of the diabetic/control groups had burn injury.

Vibe and Pless [4], found in the general population an improvement in skin graft take from 83% to 92%, percentages which are similar to those found in our control groups (Smoker's control group=85% to 93%, Diabetic's control group=79% to 88%). With the use of fibrin glue over difficult areas, their percentage of improvement was 44% to 88%. These results are higher than ours. These results are higher than ours, since the percentage of improvement we found for the smoking group was 17% (from 70% to 87%); for the diabetic group the percentage was 26% (from 58% to 84%). This difference may be due to two circumstances. First, this study included a very small population (20 patients), which lowers its accuracy. Secondly, difficult anatomic areas may have a stronger negative impact on graft take, and may benefit more from the use of fibrin glue. Analysing our results and comparing them with the results from Vibe and Pless [4], we suggest that the use of fibrin glue may counteract the negative impact of factors associated with decreased graft survival. We agree that other variables not considered in the exclusion criteria could have a direct impact on graft survival and act as additional confounding factors, like the different anatomic areas. However, to avoid this potential effect, wounds located in reported difficult area, as the axilla, perineum and gluteal folds [5] were excluded from this study. Moreover, considering the 3 types of physician criteria that we explained (always fibrin use, never fibrin use and fibrin use depending on the injury location), we assumed that the same wound located in the same area would be treated similarly by the same physician no matter if the patient was a smoker or diabetic type 2. Thus, we considered for the analysis that the anatomic areas were treated similarly in all the groups.

We hypothesize that if both factors, smoking and diabetes mellitus type 2, were present in the same patient, the negative impact would be even higher or additive, significantly decreasing the graft survival. Additionally, clarification of the mechanisms by which smoking and diabetes mellitus type 2 hinder graft take are warranted, as is the mechanism whereby fibrin glue counteracts them. We can conclude that graft loss is associated to smoking and diabetes mellitus type 2. After reviewing this data, we suggest the use of fibrin glue as a method of increasing the percentage of skin

graft survival in all the patients, especially who smoke or suffer from DM type 2. Nevertheless, future prospective, randomized, controlled clinical trials should be conducted to give stronger evidence to these results. ■

Disclosure. *Acknowledgments: We gratefully acknowledge the help of Dr. Maclenan for assisting for IRB review of the research. Financial support: none. Conflicts of interest: none.*

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