ENZYMATIC DEBRIDEMENT COMPARED TO SURGICAL DEBRIDEMENT: A COST ANALYSIS IN A BURN UNIT IN SPAIN

EXCISIONS ENZYMATIQUE ET CHIRURGICALE: ANALYSE MÉDICO- ÉCONOMIQUE DANS UN CTB ESPAGNOL

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SUMMARY. The standard care for burns is tangential surgical debridement and subsequent covering, but recently enzymatic debridement has appeared as an alternative. The objective of this study, using an individualised cost-per-patient information system, is to compare the cost per patient of these two alternatives and identify their main determining factors. A non-randomised, retrospective, observational study was carried out with 79 patients, 39 of whom were treated with surgical debridement. The average cost per patient for enzymatic debridement is lower, particularly due to a shorter length of stay of critical hospitalisation (13.7 vs. 18.9 days; €26,101 vs. €33,919), a decreased need for surgical procedures (0.45 vs. 1.28) and a shorter use of operating theatres (53 vs. 202 minutes; €904 vs. €3,000). Age, aetiology, evolution length and percentage TBSA are robust determinants of the cost of care for burn patients. The type of procedure does not appear to significantly affect the cost per patient.

Keywords: surgical debridement, enzymatic debridement, cost per patient

RÉSUMÉ. *Le traitement de référence d'une brûlure profonde est l'excision chirurgicale suivie de greffe. L'excision enzymatique se pose en alternative à la chirurgie. Nous avons comparé le coût individuel de ces 2 options, en utilisant un moyen informatique approprié. Il s'agit d'une étude observationnelle rétrospective conduite sur les dossiers de 79 patients dont 39 traités chirurgicalement. La réduction de coût calculée pour le traitement enzymatique (de 33 919€ à 26 101€) tient de la réduction de la durée de séjour (de 18,9 à 13,7 jours), de la réduction du nombre d'actes chirurgicaux (de 1,28 à 0,45) et la réduction de la durée d'utilisation du bloc opératoire (de 202 à 53 mn) ce qui génère une diminution de coût de 3 000 à 904€. Cependant, l'âge, la cause, la surface brûlée et la durée de cicatrisation sont des paramètres robustes de variation des coûts, la stratégie chirurgicale ou enzymatique semblant n'agir qu'à la marge.*

Mots-clés : *excisions chirurgicale, excision enzymatique, coût individuel*

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Manuscript: submitted 30/01/2023, accepted 16/03/2023
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Introduction

Major burns patients have a mortality rate of up to 18%, and morbidity that involves multiple functional and aesthetic alterations.[1,2] The annual incidence of patients with severe burns can be up to 2.9 cases per 10,000 inhabitants in Europe.[1] Due to the severity of the injuries, these patients need intensive, complex care in specialised units, as well as prolonged hospital stays that usually entail multiple surgical procedures and complex dressing changes, which means a significant use of resources for the major health centres specializing in this type of patient. Moreover, the greater the area affected and the deeper the burns, the greater the morbidity and mortality and the associated hospital cost. In a systematic review conducted in 2014, in which most studies considered only the hospitalisation costs, the mean cost per patient in high-income countries was estimated at €68,920.[3]

The standard care for burns is surgical debridement (SD) and subsequent covering. Full thickness and intermediate-thickness burns both have necrotic tissue, which contributes to the development of local and systemic complications, making early debridement essential for reducing these problems.

SD consists of tangential removal of the necrotic tissue using a dermatome. Due to the characteristics of the procedure and its aggressiveness, part of the dermis with the capacity to regenerate is often debrided along with the necrotic tissue, with resulting consequences and sequelae for the patients. In addition, this type of procedure requires the use of specialised resources and surgical facilities.[2,4] Recently, enzymatic debridement (ED) has appeared as an alternative to SD, with its use of a concentrate of proteolytic enzymes enriched in bromelain (NexoBrid®, Mediwound). This procedure makes it possible to carry out faster and more selective debridement of burn tissue and reduces the need for surgical debridement, causing less blood loss, reducing the total surface needing skin graft,[2,4,5] and providing a similar quality of life to the standard treatment.[2,5]

In recent years, Value-based Medicine has called for a new paradigm that requires a transformation of the traditional model. It aims to implement management of health issues based on the value provided to the patient, measured both in terms of health outcomes achieved and economic resources used.[6] In this regard, the measurement of health-care costs constitutes a fundamental element.[7] In order to know the cost of a disease, it is necessary to develop a cost model that enables healthcare providers to see the individualised cost of each patient.

The traditional cost information system for health centres is based on Diagnosis-Related Groups (DRGs), which classifies hospital patients into homogeneous groups in terms of their clinical diagnosis and resource consumption.[8] Furthermore, these traditional cost information systems obtain data through costs reported by departments or medical services, which is the traditional form of hospital management.[9] These systems calculate the costs based on the top-down method,[10] i.e. the medical service that discharges the patient assigns them the average cost of their diagnosis. This method of calculation means it is not possible to see the individualised cost per patient, which causes limitations associated with potential bias in the results of cost studies, economic evaluations and Value-based Medicine.[11] For this reason, it is necessary to have economic information systems that make it possible to find out the real, individualised cost of each patient and of each of the services received.[3]

The Ezkerraldea-Enkarterri-Cruces Integrated Healthcare Organisation (EEC IHO) has designed, developed and implemented a Cost-per-Patient Information System based on a model of real costs per patient. The system applies a bottom-up methodology[10] and connects all the sources of information generated in clinical practice, integrating healthcare information with economic information, so that the unit cost of healthcare services and the individualised cost per patient can be calculated.

The objective of this study, using an individualised cost-per-patient information system, is to compare the cost per patient of SD and ED of burn patients admitted to our Major Burn Unit, and to identify their main determining factors.

Materials and methods

Study design

A non-randomised, single centre, retrospective, observational study on 79 burn patients admitted between 2016 and 2020 was carried out. The patients in the intervention group (40) were treated with ED, while the patients of the control group (39) were treated with SD. Both groups were followed up until hospital discharge.

Since the introduction of ED at Cruces University Hospital in September 2017, all patients who met ED criteria according to the European consensus of 2017 have been given this type of debridement. Therefore, to create the control group, a review was conducted of previously treated patients who would later have been candidates for ED. Two independent doctors from the Plastic Surgery and Burn Care Department of the EEC IHO carried out a review of the medical records and photographs of all the patients admitted to the Burn Unit of Cruces University Hospital from October 2016 to April 2020. To determine the patients in this group, a review of the reports at admission and after the first 72 hours was made, as well as a review of photographs taken on admission and up to the first 72 hours afterwards. Patients in the enzymatic debridement group were grouped consecutively from the first use of the debridement product at the EEC IHO.

Ethical approval for this study was obtained from the Ethical Committee of Cruces University Hospital (EPA2019099), the Basque Clinical Research Ethics Committee.

Study subjects

A total of 79 patients were analysed, 39 of whom were treated by SD and 40 by enzymatic debridement.

The inclusion criteria were the following: patients admitted between October 1, 2016 and April 16, 2020; patients over 16 years of age; patients with partial thickness and full thickness burns, as well as areas involving mixed degrees, according to diagnostic evaluation in the first 24-72 hours after injury; patients at risk of developing compartment syndrome.

The exclusion criteria were the following; superficial burns diagnosed in the first 24-72 hours after injury; chemical burns; electrical burns; poly-traumatised patients who required surgical procedures from other services (such as Traumatology, General Surgery and Neurosurgery); patients for whom it was decided to limit therapeutic effort on admission; deceased patients; patients with known allergies to pineapple, papain-containing fruits, latex proteins, bee venom and olive pollen; registered patients without photographs or with incomplete medical reports for the first 24-72 hours.

Procedures

SD consists of removing the burn tissue using a manual or electric dermatome, so that the necrotic tissue is removed tangentially until a healthy wound bed is reached, onto which a skin graft or other options (such as artificial dermis, flaps or other methods) can be placed. An operating room is required to carry out this procedure.

Enzymatic debridement consists of the application of a mixture of proteolytic enzymes derived from bromelain, which is extracted from pineapple. These enzymes are capable of selectively debriding the necrotic tissue of partial and full thickness burns over an application period of 4 hours, leaving in situ the viable dermis with its capacity to regenerate. During the four hours of application, the patient has to be monitored and sedated, but the procedure does not require an available operating room and can be performed in the critical care unit cubicle.

Variables and outcomes

Clinical and socio-demographic patient variables including age, gender, aetiology, evolution hours, inhalation, percentage of total body surface area affected (TBSA) and the Abbreviated Burn Severity Index (ABSI) were collected on discharge.

Patient resource-use variables were defined as primary outcomes. Then, emergency visits, laboratory tests, imaging and functional diagnosis, surgery, hospitalisation, pharmacy, blood transfusion, prosthesis, rehabilitation and the use of either SD or ED were collected on discharge. Unit costs associated with each resource use were also compiled. Finally, the hospital cost per patient was computed by multiplying patient resource use by its corresponding unit costs, and defined as a secondary outcome.

Data

Clinical and socio-demographic patient information was collected from the clinical records of the Basque Country Health Service, while the resource use and unit costs were obtained from the Cost-per-Patient Information System (CPIS) of the EEC IHO.

Cost-per-patient information system (CPIS)

The EEC IHO designed, developed and implemented their CPIS based on a cost-per-patient model, using the bottom-up methodology,[10] which connects all sources of information generated in clinical practice, integrating care information with economic information. The system presents, in detail, the real cost per individualised patient throughout the care cycle and the various different clinical procedures, with the traceability of all the Real World Data (RWD) carried out in the EEC IHO, from primary care to specialised care. Patients are identified by a code, which is anonymized.

The CPIS is displayed in a Business Intelligence Tool, which is based on an analytical accounting model and is supported by a computer programme, which standardises and calculates the unit costs per patient. The system uses a bottom-up calculation method, so that most of the costs are allocated directly to the patient through the clinical episode that is generated during their treatment and care (*Fig. 1*).

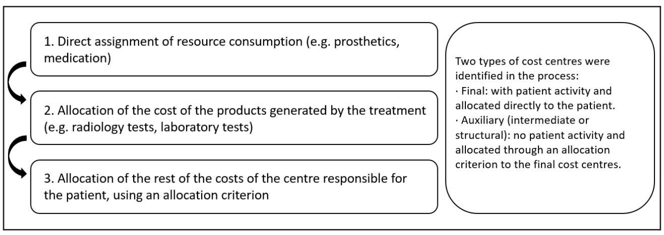

Fig. 1 - Process for obtaining the cost of each patient

The system includes information relating to the patient's disease, diagnosis and procedure, as well as socio-demographic information (age, sex and place of residence). In addition, it is divided into more than 30 factors or categories of resource consumption (e.g. hospitalisation, operating rooms, prosthetics, pharmacy, consultations, food, laboratory and radiology).

Descriptive analysis

A descriptive analysis (mean/standard deviation or frequency, correspondingly) was carried out, followed by statistical tests (t-student and chi-square, correspondingly) on clinical and socio-demographic variables, comparing the SD and ED groups. Subsequently, an identical analysis was performed on outcomes according to type of resource use and type of cost.

Regression analysis

A regression analysis was conducted exploring the determinants of the variability of the cost of major burn patients. The following linear regression was estimated by ordinary least squares (OLS):

$$LnC_i = \beta_0 + \sum_{k=1}^{K} \beta_K X_i + \mu_i$$

where LnC_i is defined as the logarithm of the cost per patient *i*. The covariates X_i define the characteristics of patient *i*, where β_0 and β_K are the constant term and parameters associated with the covariates X_i, respectively, and μ_i is the error term.

A full model including all potential covariates was firstly estimated, and a reduced model was finally estimated using a stepwise regression strategy to eliminate covariates that did not show associations with the cost per patient or multicollinearity problems. Then, the White test for heteroscedasticity and the Shapiro-Wilk test for normality were carried out. Analyses were performed in Stata v19.

Results

No statistically significant differences between the SD and ED groups before debridement were found. *Table I* shows the clinical socio-demographic characteristics of the SD and ED groups.

The mean cost per patient with SD at Cruces University Hospital is € 44,814, and € 36,519 with enzymatic debridement. This represents a reduction of € 8,295 in the cost per patient in hospitalisation after a burn. Therefore, average cost per patient for ED is lower than for SD, particularly due to a shorter length of stay (LoS) of critical hospitalisation (13.7 vs. 18.9 days; € 26,101 vs. € 33,919), a decreased need for surgical procedures (0.45 vs. 1.28) and a shorter use of operating theatre (53 vs. 202 minutes; € 904 vs. € 3,000). *Table II* shows resource use and the corresponding costs across relevant items for both the SD and the ED groups.

Regarding the results of the estimated regression models illustrated in *Table III*, model 4 is shown as

Table I - Clinical and socio-demographic characteristics

Variable		SD (n = 39)	ED (n = 40)	p-value
Male, % (n)		74.36 (29)	75.00 (30)	0.9478
Age, mean (SD)		49 (14)	44 (16)	0.1481
Aetiology, % (n)				0.0320
	Flame	76.92 (30)	52.50 (21)	
	Scald	12.82 (5)	37.50 (15)	
	Contact	0 (0)	5.00 (2)	
	Electrical	5.13 (2)	5.00 (2)	
	Other	5.13 (2)	0 (0)	
Evolution hours, % (n)				0.1350
	< 2 hours	61.11 (22)	37.50 (15)	
	2 - 6 hours	27.78 (10)	52.50 (21)	
	7 - 24 hours	8.33 (3)	5.00 (2)	
	> 24 hours	2.78 (1)	5.00 (2)	
With inhalation, % (n)		35.90 (14)	35.00 (14)	0.9336
% TBSA, mean (SD)		14.60 (12.89)	11.81 (12.66)	0.3348
% Deep burn, mean (SD)		10.08% (13.73)	1.84% (2.77)	0.0004
ABSI, % (n)				0.4670
	2-3	5.13 (2)	12.50 (5)	
	4-5	38.47 (15)	45.00 (18)	
	6-7	43.59 (17)	32.50 (13)	
	8-9	7.69 (3)	7.50 (3)	
	10-11	2.56 (1)	2.50 (1)	
	>11	2.56 (1)	0 (0)	

SD: Surgical debridement; ED: Enzymatic debridement;
ABSI: Abbreviated Burn Severity Index; TBSA: total body surface area

the best-adjusted model (adjusted R-squared: 0.60) as it is robust through the stepwise regression strategy (Model 1 to Model 4). Model 4 showed the age, the type of aetiology, the evolution length and the percentage of TBSA as robust determinants of burn-care patient cost. Among socio-demographic factors, age appeared to increasingly affect cost per patient. Focusing on clinical factors, patients with contact burns incurred higher costs per patient compared to other types of aetiology. In terms of evolution length, attending the healthcare centre between 2 and 6 hours raised the cost per patient compared to longer evolution lengths, and as expected, an increase in burned body surface area resulted in a higher cost per patient. Among the non-significant factors, it is noted that the type of intervention seemed not to significantly affect the cost per patient.

Discussion

This article carries out a cost study comparing two alternative treatments in burn patients, SD and ED, and, in addition, offers evidence on the main determining factors of this cost, based on a highly advanced individualized cost-per-patient information system.

The mean cost per patient with SD at Cruces University Hospital represents a difference of €8,295 in the cost per patient in hospitalisation after burns, compared to ED (€44,814 vs. €36,519). These results are similar to those reported in a study published by Giudice et al.,[4] with a reduction in cost per patient of €5,330 due to enzymatic debridement (€38,848 vs. €33,518). Further, other authors have published lower costs than those in our study. In Spain, Martínez-Méndez et al.[12] reported a mean cost per patient of €20,844 in patients treated at the Burn Unit in La Paz University Hospital in Madrid. Similarly, Sanchez et al.[13] calculated direct costs of €16,296 for La Fé University Hospital. In other health systems, Jenda Hop et al.[14] reported mean direct costs of €21,168 for patients with a mean burned area of 8% in the Netherlands. For patients from Finnish hospitals, Koljonen et al.[15] reported a mean cost of €35,028, but with a mean follow-up of 66 months. This difference in cost per patient may be due to the use of different methodologies, perspectives or approaches to costs (such as top-down or bottom-up systems, or follow-up) or the use of estimates instead of real costs. The Cost-per-Patient Information System provides exhaustive data and gives the individualised cost per patient of each of

Table II - Resource use and costs

	Resource Use		Costs (Euros)	
	Mean (Standard deviation)			
	SD (n = 39)	ED (n = 40)	SD (n = 39)	ED (n = 40)
Emergency department (visits)	0.97 (0.03)	0.92 (0.04)	364 (61)	391 (124)
Critical hospitalisation (days)	18.90 (16.00)	13.7 (10.65)	33,919 (29,199)	26,101 (20,992)
Hospitalisation (days)	4.77 (5.00)	5.87 (5.73)	1,765 (1,893)	2,975 (3,566)
Surgical procedures (procedures)	1.28 (1.26)	0.45 (0.55)	N.A.	N.A.
Operating theatre (min.)	201.92 (256.49)	52.82 (73.35)	3,000 (4,088)	904 (1,242)
Nexobrid® (percentage of patients)	0 (N.A)	100 (N.A.)	0 (0)	1,693 (1,335)
Diagnostic tests (tests)	29.03 (22.63)	21.80 (16.62)	1,263 (1,273)	1,112 (1,053)
Other[1] (percentage of patients)	100 (N.A)	100 (N.A.)	3,667 (4,608)	2,610 (3,422)
Home hospitalisation (days)	0.23 (1.44)	1.57 (9.96)	24 (150)	191 (1,207)
Specialist visit (visits)	5.00 (5.26)	4.67 (4.00)	270 (275)	285 (320)
Rehabilitation (sessions)	6.36 (11.30)	3.17 (5.65)	542 (997)	257 (544)
Total	N.A.	N.A	44,814 (38,476)	36,519 (26,399)

SD: Surgical Debridement; ED: Enzymatic Debridement; N.A.: Not Applicable
[1] 'Other' includes the cost of antibiotic therapy, specific medication, wound-dressing management, mechanical breathing and blockages. All patients have consumed at least one of these resources.

Table III - Cost regression models

	Dependent variable *Logarithm of cost per patient*			
Models	**Model 1**	**Model 2**	**Model 3**	**Model 4**
Explanatory variables	**Coefficient (SE)**			
Enzymatic debridement (Yes)	-0.0866 (0.1770)	-0.0851 (0.1738)	-0.0768 (0.1737)	-
Age (in years)	0.0142** (0.0045)	0.0141** (0.0045)	0.0138** (0.0043)	0.1632*** (0.0041)
Gender (Female)	-0.0489 (0.1497)	-	-	-
Aetiology				
Scald	-0.0867 (0.1825)	-0.0926 (0.1737)	-0.1520 (0.1579)	-0.2085 (0.1422)
Contact	0.9148*** (0.1410)	0.9226*** (0.1319)	0.9300*** (0.1746)	0.8384*** (0.1520)
Electrical	0.0059 (0.1511)	0.0178 (0.1511)	0.0309 (0.0995)	-0.0815 (0.07922)
Other	-0.3849 (0.5271559)	-0.3452 (0.5258)	-0.4373 (0.5177)	-0.4009 (0.5197)
Evolution hours				
2-6 hours	0.2133 (0.1584)	0.2235 (0.1584)	0.2144 (0.1727)	0.2667** (0.1293)
6-24 hours	0.0565 (0.1482)	0.0646 (0.1513)	0.0699 (0.1554)	0.0827 (0.1549)
>24 hours	-0.6919 (0.5081)	-0.6885 (0.5134)	-0.6231 (0.5266)	-0.6385 (0.4973)
Inhalation (Yes)	0.1668 (0.1443)	0.1692 (0.1439)	-	-
Total body surface area (%)	0.0382*** (0.0042)	0.0383*** (0.0043)	0.0401*** (0.0042)	0.0404*** (0.0044)
Intercept	9.0813 (0.2377)	9.0616 (0.2440)	9.1299 (0.2351)	9.0500 (0.2213)
Observations	79	79	79	78[b]
Adjusted R-squared	0.58	0.58	0.58	0.60

SE: standard error
a White test of heteroscedasticity (p-value=0.704) and Shapiro-Wilk p-value of normality (p-value=0.905)
b Dropped outlier observation observed in the Shapiro-Wilk test of normality in Model 3
***p-value<0.01; **p-value<0.05; *p-value<0.1

the resources used for the patient's healthcare without estimates and in a way that is closer to reality. Other data systems are underestimating the average cost per patient. A study published by Kern et al.[16] estimated a 30% reduction in cost per patient in patients with 5% total body surface burns as a result of the use of enzymatic debridement. If the percentage of total body surface burned was 15%, however, the costs per patient for enzymatic and surgical debridement were similar. To obtain the cost per patient, they used the classification system of Diagnosis-Related Groups and results data published by Rosenberg.[2] Moreover, it should be noted that in recent years, the number of major burn patients has decreased and there is a trend towards less severity and extent of burns in this geographical area of reference.

As a result of the regression model, age, aetiology, evolution length and percentage of TBSA are shown as robust determinants of burn-care patient cost. In particular, burns due to contact with hot surfaces increase the cost compared with other aetiologies. This type of burn, although it rarely causes burns with large TBSA, usually involves a deeper burn and therefore requires more surgical time, which ultimately raises costs. Regarding the time elapsed from the accident to their arrival at our centre, according to the regression model, patients arriving within the first 2-6 hours after the accident incur higher costs than patients arriving less than 2 hours and more than 24 hours after the accident. Patients with 2-6 hours of evolution length are mostly (80%) transfers from other regions due to burn severity, and this might explain why this evolution length increases the burn-care patient cost. Additionally, although a higher evolution length might intuitively be expected to raise the cost, those with more than 24 hours' evolution length are not severe and are admitted into hospital later than other patients. Finally, although differences in the estimated patient cost of both types of procedure (ED vs. SD) have been found, the regression model does not report the type of procedure as a statistically significant factor of the burn-care patient cost. These *a priori* conflicting results may be explained by the high variability observed between the estimated patient cost of both types of procedure, showing variation coefficients of 0.86 and 0.73, for ED and SD respectively.

Differences noted in the deep burn extension in each group, which are more extensive in the SD group, can be explained due to the use of ED as both a treatment and diagnostic tool. Clinical evaluation has proved to be accurate in only 60-75% of cases,[17] and for clinical purposes in this study, we considered all areas that subsequently needed coverage to be "deep burns". For the ED group, diagnosis of the depth of the burn is more accurate and can be determined at the moment of its removal.

One limitation of this study is that patient costs do not include the social costs of burn patients. For some patients of this type, indirect costs can represent a significant part of the total cost, which can include sick leave and physical and psychological sequelae. Sánchez et al.[13] published an annual cost per burned patient of €83,144, including indirect costs. For the Netherlands, Jenda Hop et al.[14] reported a mean cost of €26,540 per patient for patients with a mean burned area of 8%, including sick leave costs.

Moreover, we consider that it is a limitation to have studied patients admitted to one single hospital. The clinical practice of one specific major burn service can significantly determine the average cost of patients treated. It would therefore be necessary to carry out this study with patients from other health organisations.

Lastly, it should be noted that Cruces University Hospital does not have intermediate care in the Major Burns Service, but instead has intensive care in the Burn Unit or hospitalisation in the Plastic Surgery general ward. As treatment by ED is less aggressive than by SD, the availability of an intermediate care unit seems recommendable for the care of these patients, since at present a certain number of them do not require admission to a critical care unit. The existence of an intermediate care unit could reduce the average stay and cost per patient.

Next steps

Given the usual lack of availability of information about real costs per patient, it is necessary to make advances in this area of health results by comparing costs and results of the different therapeutic alternatives available, so as to guide clinical practice towards those activities that generate the best health results for each resource unit consumed (Value Based HealthCare equation), where better results are the results that really matter to the patient. This will make it possible to put the patient at the centre of the system and apply healthcare practice in a way that moves towards value-based medicine.

Conclusions

The cost per major burn patient under ED is lower than under SD. The predictors of the cost per patient are type of aetiology, evolution length and burned body surface. The type of procedure seems not to significantly affect the cost per patient.

Against a background of increasing availability of data in health organisations, it is necessary to carry out studies with Real World Data from individualised patients to complement the evidence generated in clinical trials, and enable us to find out the effectiveness and safety of the different technologies or procedures available, as well as their cost, in patients in routine clinical practice.

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