The Influence of the Socioeconomic Status and the Density of the Population on the Outcome After Peripheral Artery Disease

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Abstract

Background. Low socioeconomic status (SES) and living in a rural environment are associated with poorer health and a higher number of amputations among the population at large. The purpose of this study is to determine the influence of low SES and of the degree of urbanization on the short-term and long-term results of patients after revascularization for peripheral artery disease.

Methods. An observational retrospective follow-up study of 770 patients operated on for peripheral artery disease at three university centers in north-western Spain from January 2015 to December 2016. The events studied were Rutherford classification of severity upon admission, direct amputation, amputations in the follow-up period, new revascularization procedures, major adverse cardiovascular events (MACE), and overall mortality. Mean personal income and income of the household associated with the street in which each patient lived and the degree of urbanization in three areas as per Eurostat criteria: densely populated areas, intermediate density areas, and thinly populated areas. Comorbidity, surgical, and follow-up variables were also collected. Descriptive analysis and Cox regression were used. Approval was obtained from the regional ethics committee.

Results. Median follow-up was 47.5 months. MACE occurred in 21.5% of the series and overall mortality was 47.0%. Living in a thinly populated area is associated with a lower risk of MACE (adjusted subhazard ratio = 0.60; 95% confidence interval [CI]: 0.39–0.91). Overall survival is

lower in intermediate density area patients (adjusted Hazard Ratio = 1.46; 95% CI: 1.07–2.00). The third quartile of mean personal and household income is associated with a higher risk of major amputation at follow-up (adjusted Odds Ratio 1.92, 95% CI: 1.05–3.52 and adjusted Odds Ratio 1.93, 95% CI: 1.0.3–3.61, respectively).
Conclusions. Patients who live in a densely populated area run a higher risk of MACE. SES is neither associated with worse outcomes after surgery nor with MACE in long-term follow-up.

Keywords: flap prefabrication; mesenchymal stem cells; skin substitutes; seeding; tissue engineering

INTRODUCTION

Low socioeconomic status (SES) is associated with poorer health,[1,2] higher cardiovascular risk,[3] and shorter life expectancy.[4] As regards, peripheral artery disease (PAD), higher amputation rates,5, 6, 7 and an increase in major adverse limb events after infrainguinal surgery have been reported in more disadvantaged sectors of the population.[8] Indeed, some authors consider primary amputations (without attempted revascularization) as a marker of poor quality, of difficulties in accessing the health system, and even of bias in healthcare by their doctors.[9,10] Patients with PAD, moreover, run a higher risk of long-term mortality than the general population because of the systemic nature of arteriosclerosis. Major adverse cardiovascular events (MACE) determine the long-term prognosis in this cohort and include myocardial infarction, stroke, and cardiovascular death.[11]

Although the definition of low SES may vary among authors and cultures, there are four common components: income level, educational attainment, employment status, and environmental factors such as type of neighborhood.[12] The Spanish National Institute of Statistics recently published a Household Income Distribution Map, a project that details mean personal and household income of every district in Spain.[13] This information on a district's nature is complemented with degree of urbanization (DEGURBA) classification, which was designed by the European Statistical Office (Eurostat).[14] There are no studies on the influence of both tools on the prognosis of patients with PAD in Spain.

The objective of this study is to determine the influence of a neighborhoods' income and its DEGURBA on the MACE rate and on mortality in the long-term follow-up of patients admitted for the first time for PAD at three university centers in northwest Spain. Other outcomes, such as Rutherford classification, direct amputation, new revascularization procedures, and amputation at follow-up were also examined.

PATIENT POPULATION AND METHODS

Data were collected prospectively on patients operated on for PAD at three university hospitals in northwest Spain from January 2015 to December 2016. Follow-up continued until January 2020. All patients who underwent lower limb revascularization or major amputation were included. Cases with revascularization leading to amputation in the same hospital admission and those patients previously operated on for PAD in the same leg were excluded. This exclusion ensured a correct comparison among groups and avoided potential biases (patients incorrectly selected for revascularization or early amputations on account of technical errors). Cases with acute ischemia were likewise excluded. The study was approved by the A Coruna-Ferrol clinical research ethics committee (code 2020/144).

Data were collected on mean personal income and the mean family income associated with the street in which each patient lived at the time of hospital admission. This information was obtained from the Household Income Distribution Map, published by the Spanish National Institute of Statistics in conjunction with the Spanish Tax Office and the regional tax authorities. The Household Income Distribution Map offers data on more than 99.8% of the resident population of Spain.[13] Income was distributed in quartiles, the first of which corresponded to the lowest income and the fourth to the highest.

Patients' municipalities of residence were identified to determine the DEGURBA. The Instituto Galego de Estatística, following Eurostat's (reference) DEGURBA criterion, classified municipalities into three groups: densely populated areas (DPAs), intermediate density areas (IDAs), and thinly populated areas (TPAs).[15] DPAs are areas with more than 50,000 inhabitants or in which more than 50% of the population live. IDAs are towns and suburbs with more than 5,000 inhabitants or in which less than 50% of the population live in DPA or less than 50% live in TPA. TPAs are rural environments.

Variables were collected on comorbidity, surgical, and follow-up and on patients' gender and age. The following were collected as comorbidity variables: hypertension, dyslipidemia, diabetes mellitus, active smoking, coronary artery disease (history of ischemic angina, myocardial infarction, or coronary revascularization), chronic renal failure, dialysis, and chronic obstructive pulmonary disease.

The surgical variables were previous revascularization in the contralateral leg, Rutherford classification upon admission, direct amputations and level of amputation, revascularization type (open or endovascular), and treated sector (aortoiliac, femoropopliteal, or distal). Cases of hybrid surgery or treatment in multiple sectors were recorded as open surgery and proximal sector.

Follow-up variables were medical treatment with antiplatelet agents and statins, fitting of patient prostheses, new revascularization procedures, and major amputations that occurred during follow-up.

Studied Events

The events studied were mortality or the presence of MACE in the long-term follow-up of this cohort. The term MACE has been defined previously as an event that encompasses acute myocardial infarction and/or stroke and/or cardiovascular death (fatal stroke, fatal acute myocardial infarction, fatal congestive heart failure, sudden cardiac death, and death due to ruptured aortic aneurysm).[11] Arterial disease severity (Rutherford classification), direct amputation in the same hospital admission, major amputations during follow-up, and new revascularization procedures were also studied.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation. Qualitative variables were expressed as frequencies and percentages.

A univariate analysis was performed comparing patients' basal characteristics, surgical variables, and events in the follow-up as per (i) the DEGURBA, (ii) quartiles of income per person, and (iii) quartiles of household income. Mean comparisons were evaluated with the KruskalleWallis test, after normality testing using the Kolmogorove Smirnov test. The association between qualitative variables was tested with the chi-squared test.

Overall survival after surgery was analyzed using KaplaneMeier curves and bivariate log-rank tests. In turn, the cumulative incidence of MACE in the follow-up was estimated considering death as a competing risk, using the method proposed by Kalbfleisch and Prentice.[16] MACE cumulative incidence was compared across different groups of patients using Gray's test.[17]

Finally, to analyze the independent association of DEGURBA and levels of income with the outcomes studied, a multivariate analysis was performed. For dichotomous outcomes, a multivariate logistic regression analysis was performed. In turn, a multivariate Cox proportional hazards model and the model proposed by Fine and Gray[18] were adjusted when overall survival and MACE incidence were considered as the outcome, respectively. In all cases, multivariate models were adjusted for predefined cofounders (age, gender, smoking, diabetes, ischemic heart disease, hypertension, dislipemia, chronic kidney disease, and hospital center).

Statistical analysis was performed with SPSS version 25.0 (IBM Corp., Armonk, New York) and R 4.0.3 (www.r-project.com), with the survival and cmprsk packages added. Bilateral P values < 0.05 were considered as statistically significant.

RESULTS

Seven hundred seventy patients were included during the study period. Average age at the time of surgery was 70.6 ± 11.9 years, 76% of whom were male. Mean personal income was 11,133.4 ± 2,380.6 euros and mean household income was 27,704.6 ± 6,457.9 euros. 50.6% of the patients lived in DPA, 29.3% in TPA, and 20.1% in IDA. TPA patients had a mean personal income ($P < 0.001$) and household income ($P < 0.001$) significantly lower than IDA or DPA patients.

82.4% of patients were Rutherford classification stage 4e6, with direct amputation performed in 145 (18.9%) subjects. Patient characteristics in relation to the variables of comorbidity, surgery, and follow-up by population density are shown in Table I. These same characteristics by personal income and average household income are shown in Tables II and III, respectively.

No differences were observed in the distribution by age and by gender of patients according either to the population density of their area of origin or to income bracket. Nor were they observed in terms of the frequency of most comorbidities considered, although a significantly higher incidence of dyslipidemia was observed in patients with a higher personal income (57.0% in the first quartile, 58.9% in the second, 66.8% in the third, and 69.8% in the fourth; $P = 0.024$). Likewise, a higher incidence of hypertension was observed as the income quartile per household increased (66.3% in the first quartile, 70.8% in the second, 74.6% in the third, and 77.1% in the fourth), although the differences were not statistically significant ($P = 0.096$). In turn, a significantly higher percentage of patients with Rutherford classification ≤ stage 3 were observed in the IDA (29.2%) than in DPA and TPA (14.7%) ($P < 0.001$) and among patients in the highest estimated personal income bracket (13.5% in the first quartile, 16.1% in the second, 16.6% in the third, and 24.0% in the fourth; $P = 0.045$). No differences were detected in terms of surgical variables, either by population density or by income level. Finally, regarding treatment prescribed after surgery, a higher prescription of statins was observed in the DPA (83.0%) than in the IDA (80.5%) and the TPA (74.1%) ($P = 0.031$).

After adjustments for age, gender, smoking, comorbidities, and hospital center, in a multivariate analysis, IDAs were significantly associated with milder stages of PAD, as per Rutherford classification (adjusted odds ratio [aOR] = 0.44; 95% confidence interval [CI]: 0.27–0.72). This same tendency is observed in patients with personal income in the highest quartile (aOR = 0.50; 95% CI: 0.28–0.89) and household income in the second quartile (aOR = 0.54; 95% CI: 0.30–0.98) (Table IV).

Mean follow-up of the cohort was 39.6 ± 22.4 months and its median was 47.5 months. During this time, 136 (21.9%) patients required new revascularization procedures, followed by amputation in 105 (17.2%) cases. As regards the need for new revascularization procedures, no differences were observed by population density or among different income brackets. In contrast, after adjusting for potential confounders, a tendency toward higher amputation rates at follow-up was observed in the third quartile for both personal income (aOR = 1.92; 95% CI: 1.05‒3.52) and household income (aOR = 1.93; 95% CI: 1.03‒3.61) (Table IV).

In the cohort studied as a whole, there were 164 (21.5%) MACE during follow-up, with 362 (47.0%) patient deaths. The cumulative incidence of MACE and overall mortality at follow-up, by population density and income bracket, are shown in Figures 1 and 2. The cumulative incidence of MACE was 7.5% at 1 year, 13.2% at 2 years, and rose to 22.2% at 5 years. After adjusting for potential cofounders in the multivariate analysis, the cumulative incidence of MACE at follow-up was significantly lower in TPA (adjusted subhazard ratio = 0.60; 95% CI: 0.39‒0.91) compared to DPA, with no differences as per either personal or household income levels (Table IV).

In turn, the probability of overall survival after surgery was 80.0% at 1 year, 67.7% at 2 years, and 49.3% at 5 years. After multivariate analysis, survival was lower in IDA (adjusted hazard ratio [aHR] = 1.46; 95% CI: 1.07‒2.00) than in DPA and a similar trend was observed in TPA (aHR = 1.25; 95% CI = 0.98‒1.59), albeit not statistically significant. No differences in overall survival by income level were observed, except in the second quartile of household income, where survival was significantly lower (aHR = 1.39; 95% CI = 1.04‒1.86) (Table IV).

DISCUSSION

This multicenter retrospective study examined the influence of SES (using personal and household income as proxies) and the degree of neighborhood urbanization on short-term and long-term events in 770 postoperative PAD patients. There are three main findings: low SES is not associated with worse results after surgery or higher mortality in followup, patients who live in a TPA have a lower risk of MACE in long-term follow-up (aSHR =

0.60; 95% CI: 0.39–0.91), and patients who live in an IDA are associated with lower overall survival (aHR = 1.46; 95% CI: 1.07–2.00).

In this sample, patients in both the fourth quartile of personal income and in the second quartile of household income manifest milder stages of PAD (Rutherford ≥ 4 aOR 0.50, 95% CI: 0.28–0.89 and aOR 0.54, 95% CI: 0.3–0.98, respectively). However, worse results after surgery or a higher number of MACE or lower overall survival were not found in neighborhoods with lower personal or household income. In fact, patients in the third quartile of personal and household income had a higher risk of major amputation at follow-up (aOR 1.92, 95% CI: 1.05–3.52 and aOR 1.93, 95% CI: 1.0.3–3.61, respectively). In the sample studied, there is therefore no socioeconomic gradient associated with adverse events.

Davie-Smith et al.,[5] in a study of amputations made in Scotland, did not find any association between low SES and mortality after surgery. Most of the literature reviewed nevertheless describes this phenomenon. Hence, Stringhini et al.,[4] in a meta-analysis of more than 48 prospective studies with 1.7 million patients, concluded that low SES was associated with overall mortality and was responsible for 1 to 2 years of life lost from the ages of 40 to 85 years. In the United States, the Atherosclerosis Risk in Community study showed that living in deprived neighborhoods was associated with coronary heart disease, even after adjusting for personal income, educational achievement, and employment status.[19] Some European groups have pointed to an increased risk of cardiovascular disease and major amputations in the most disadvantaged sectors of society.[6,7,20] This new risk factor, social rank, is defined as a deprivation of material resources that limits the choice of healthier lifestyles.[21]

There are several factors that may explain our findings. First, one of the strengths of this study is that we included data on the sector in question, the revascularization type, and new revascularization procedures during follow-up, thus enabling us to compare groups more precisely. Hughes et al. only distinguish between open and endovascular;[22] Hawkins et al.[8] did not include endovascular procedures in their study; and in the Venermo et al.,[6] there is no variable on revascularization. Second, there is a higher incidence of dyslipidemia in the quartiles with the highest personal income (68.9% in the fourth quartile compared to 57% in the first, $P = 0.024$) and of hypertension in the quartiles with the highest household income (albeit not statistically significant), which would increase cardiovascular risk. Unlike other authors,[5,16,23] we found no differences in the prevalence of smoking or diabetes among groups. Third, in Spain the health system is public, free, and universal. There are therefore not the problems of access or health insurance cover that are common in the United States. Fourth, the demographic and ethnic characteristics of our population are very similar. Several studies have shown the amplifying effect of race/ethnicity on health inequality and amputation rates among African Americans and Hispanics have been established as double those among the Caucasian population.[24-26] Fifth, many studies use postcode as a proxy for income.[7,8,22] In our case, the Household Income Distribution Map[13] details the income of each street and allows for a more precise analysis. Sixth, the mean age of the sample is 70.6 years, which is significantly higher than in other publications.[5,8,27] Subjects are therefore retired and Spain is one of the countries in Europe with the highest net pension retirement rates.[28]

PAD is a known prognostic factor for short-term and medium-term cardiovascular events. In the Reduction of Atherothrombosis for Continued Health registry,[29] the MACE rate for patients with PAD was 21.1% per year. In our series, 12 months after discharge from hospital, it was 7.5%. The low event rates in this cohort can be explained by the higher percentage of patients with antiplatelet agents (95.8%) and statins (79.9%) than in the

Reduction of Atherothrombosis for Continued Health registry (78.6% and 69.3%, respectively).

We found no differences among MACE in followup either by personal or household income. As for PAD, evidence is scarcer, although low SES has been linked as an independent factor of MACE 12 months after coronary angioplasty and with a higher rate of hospital readmissions.[30,31] This has been attributed to differences in the prescription of statins and other drugs such as beta-blockers and angiotensin-converting enzyme inhibitors.[32,33] In our sample, there is uniform distribution of antiplatelet agents and statins in the four quartiles of personal and household income.

As for the higher number of MACE in the DPA (Fig. 1), some authors attribute it to environmental factors such as the lower number of open spaces in which to walk, the high prices of healthy foods in cities, or less social cohesion.[34,35] Others have expressed exactly the opposite and described worse overall health in rural populations due to (economic and geographical) barriers to using the health system and an aging population, especially in the United States.[36,37] In our case, although we observed no differences in the demographic characteristics of the different population areas, we did observe more widespread ischemic heart disease and dyslipidemia ($P = 0.052$ and $P = 0.07$) in the DPA, which would explain the increased risk of MACE in this group.

Overall survival is lower among patients who live in IDA (aHR = 1.46) (Fig. 2). It is hard to find a plausible explanation for this difference. IDA patients who underwent surgery had lower Rutherford classifications (29.2% with Rutherford ≤ 3 compared to 14.7% in DPA and TPA) ($P = 0.031$) and have higher incomes than TPA patients ($P < 0.001$). One hypothesis is that the sample size is small, as IDA only account for 20.1% of the cohort studied. Another explanation may be that the studies only differentiate between rural and urban areas and include IDA in one of these two groups. This author has not found examples in the literature of the relationship between long-term outcomes after PAD and living in IDA.

This study has some limitations. Using neighborhood personal income as an indicator of SES meant the assumption that residents in the same street have similar incomes. We think this is a normal practice but it could be wrong in some cases. Household income was not adjusted by the number of household members, although it has been shown that this does not influence health inequality.[27,38] Neither were patients from private centers included, although the number of complex arterial patients not treated in the public system is minimal. Although all patients were included on a database prospectively, some of the study variables were collected retrospectively. There were no changes in risk factors or changes in treatment throughout follow-up that could alter individual risks.

CONCLUSION

Patients who live in a DPA run a higher risk of MACE. These patients are not, however, associated with lower overall survival. SES is neither associated with worse outcomes after surgery or with MACE in long-term follow-up. Our findings show a homogeneous distribution in the treatment of PAD patients in the four income quartiles and in the three geographic distribution areas. In the sample studied, we did not observe the effect of social rank. Future studies with populations from other centers and with a larger number of patients are required to confirm our results.

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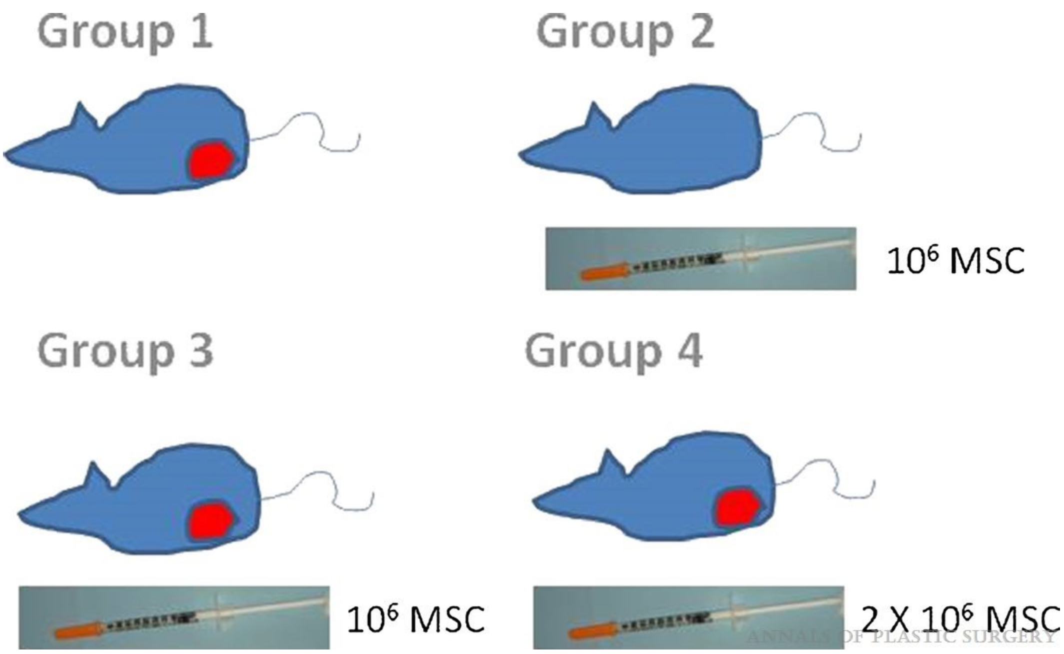

FIGURE 1

Assignment of experimental animals. Group 1: a prefabricated groin flap (GF) with biobrane was harvested without cell injection. Group 2: 1 million MSC were injected subcutaneously without flap harvesting. Group 3: a prefabricated GF with biobrane was harvested and 1 million MSC were injected subcutaneously. Group 4: a prefabricated GF with matriderm was harvested and 2 million MSC were injected subcutaneously.

FIGURE 2

Subcutaneous injection of mesenchymal stem cells in the area corresponding to the groin flap.

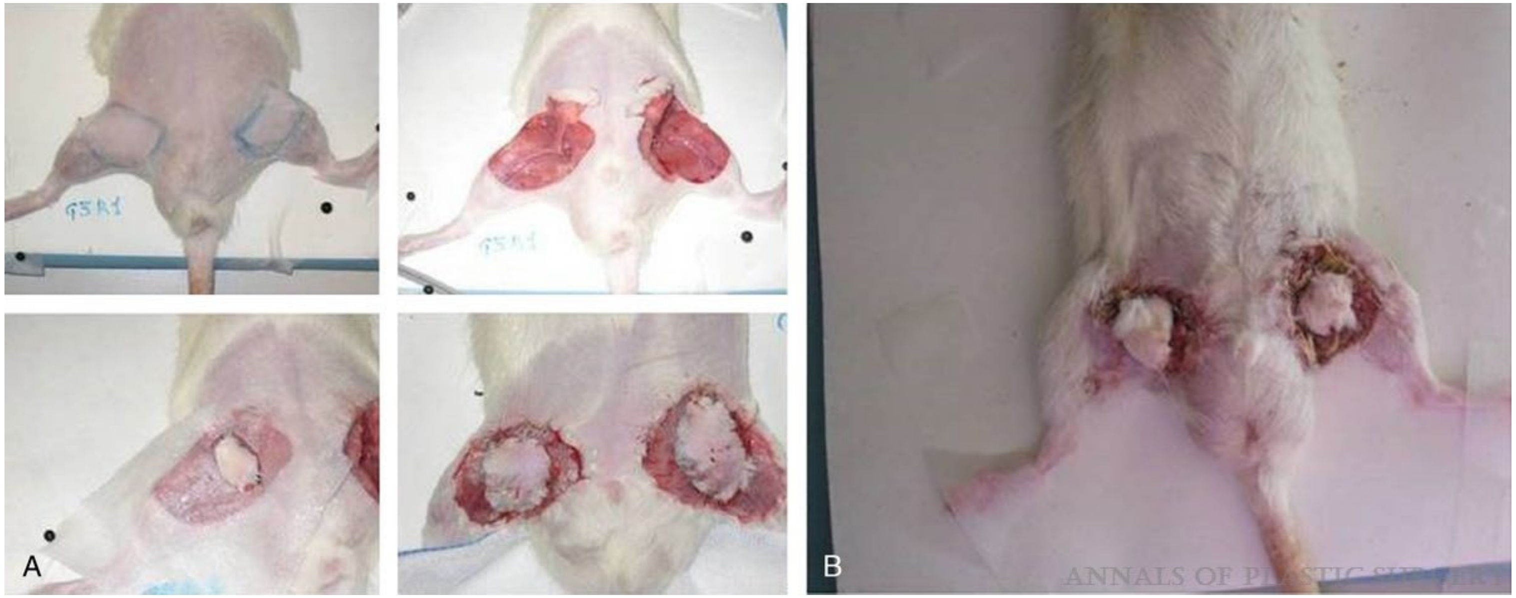

FIGURE 3

A, Sequence of the surgical technique of the prefabricated groin flap with skin substitutes. The flap is harvested as an island flap where the pedicle is isolated (above, right) and then skin substitutes are placed under and around the flap that is attached only by the vascular pedicle. B, Viability of the flaps after two weeks.

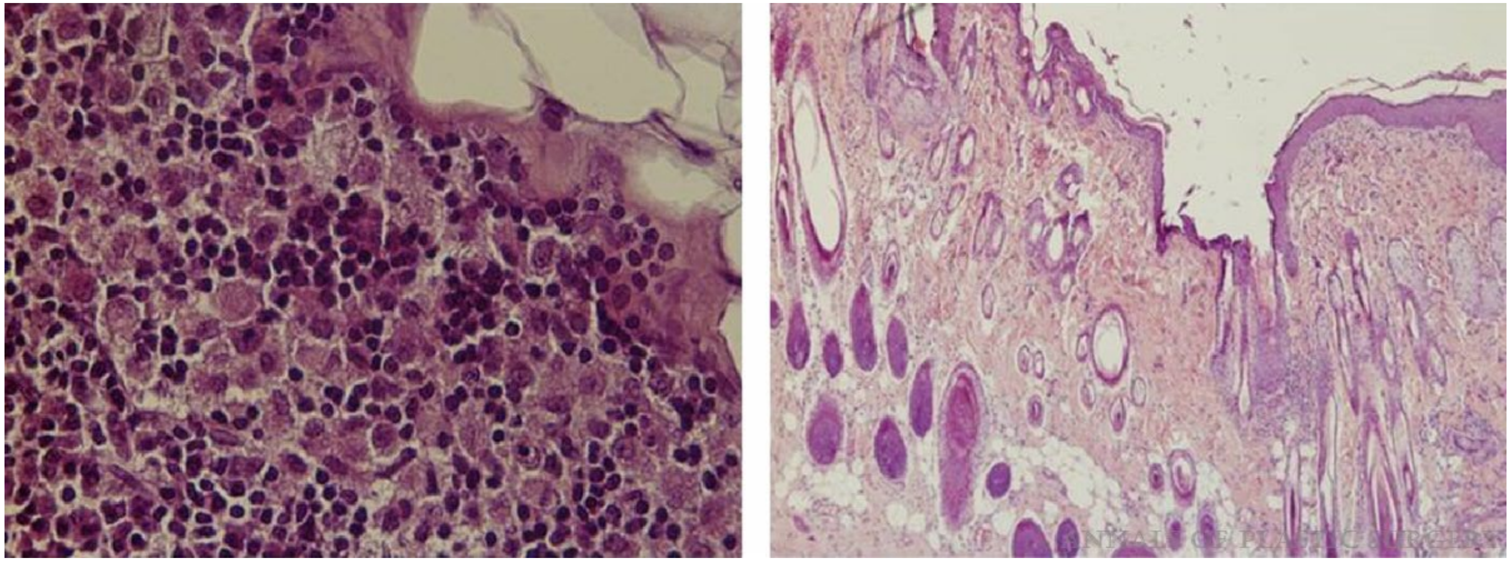

FIGURE 4

Photomicrographs of histological sections of the flaps stained with hematoxylin-eosin. Infiltration of inflammatory cells (left) and tissue viability was noted in all groups where flap was harvested.

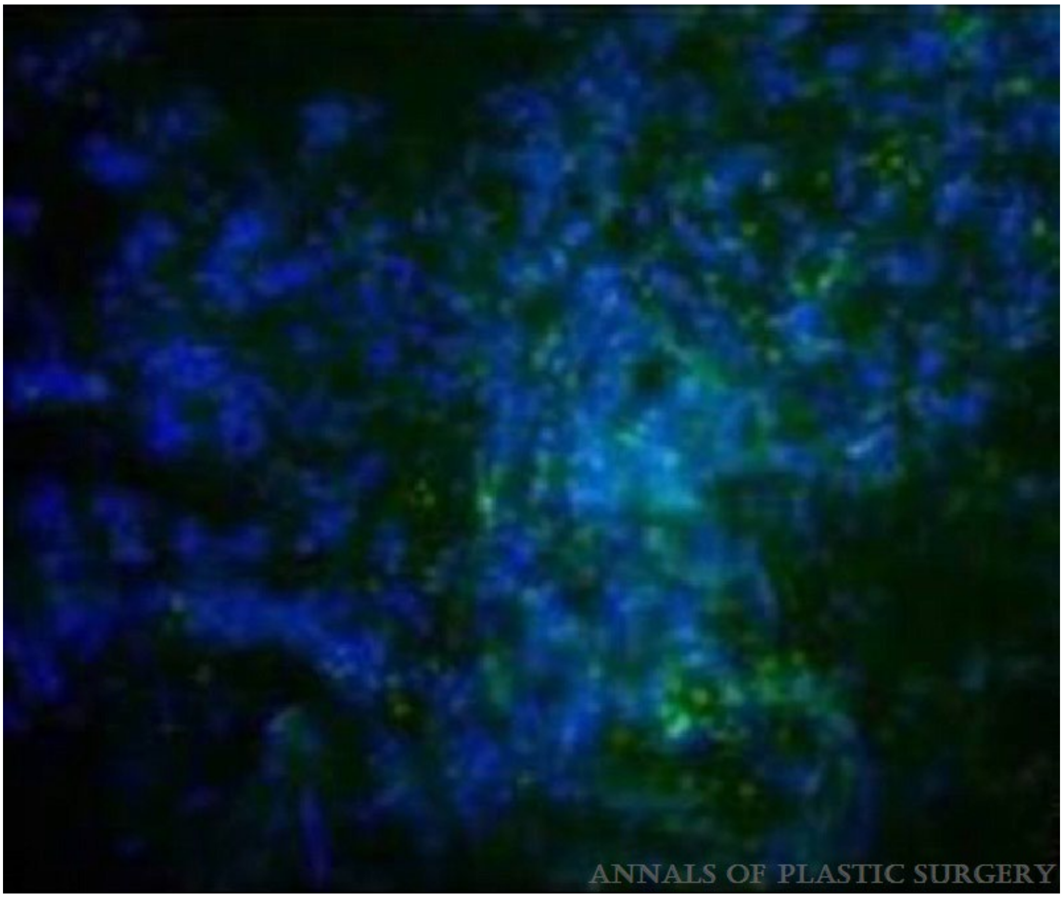

FIGURE 5

Fluorescence image showing detection of the mesenchymal stem cells by enhanced green fluorescent expression.

Group 2			Group 3			Group 4		
Rat	Side	Densitometry Values in AU DiO/Dapi	Rat	Side	Densitometry Values in AU DiO/Dapi	Rat	Side	Densitometry Values in AU DiO/Dapi
1*	Right	—	1	Right	0.46	1	Right	0.70
	Left	—		Left	0.45		Left	0.68
	Mean	—		Mean	0.45		Mean	0.69
2	Right	0.32	2	Right	0.40	2	Right	0.47
	Left	0.36		Left	0.42		Left	0.49
	Mean	0.35		Mean	0.41		Mean	0.48
3	Right	0.40	3	Right	0.50	3	Right	0.43
	Left	0.34		Left	0.49		Left	0.47
	Mean	0.37		Mean	0.50		Mean	0.45
4	Right	0.40	4	Right	0.47	4	Right	0.50
	Left	0.38		Left	0.45		Left	0.42
	Mean	0.39		Mean	0.46		Mean	0.46

*There was no detection of MSC-DiO-positive cells in rat 1 in group 2.
AU indicates arbitrary units.

TABLE 1

Densitometry Values in Each Group as Expressed as the Percentage of Positive Cells for DiO Studied for Microscopy Analysis in Relation With Positive Cells for Dapi

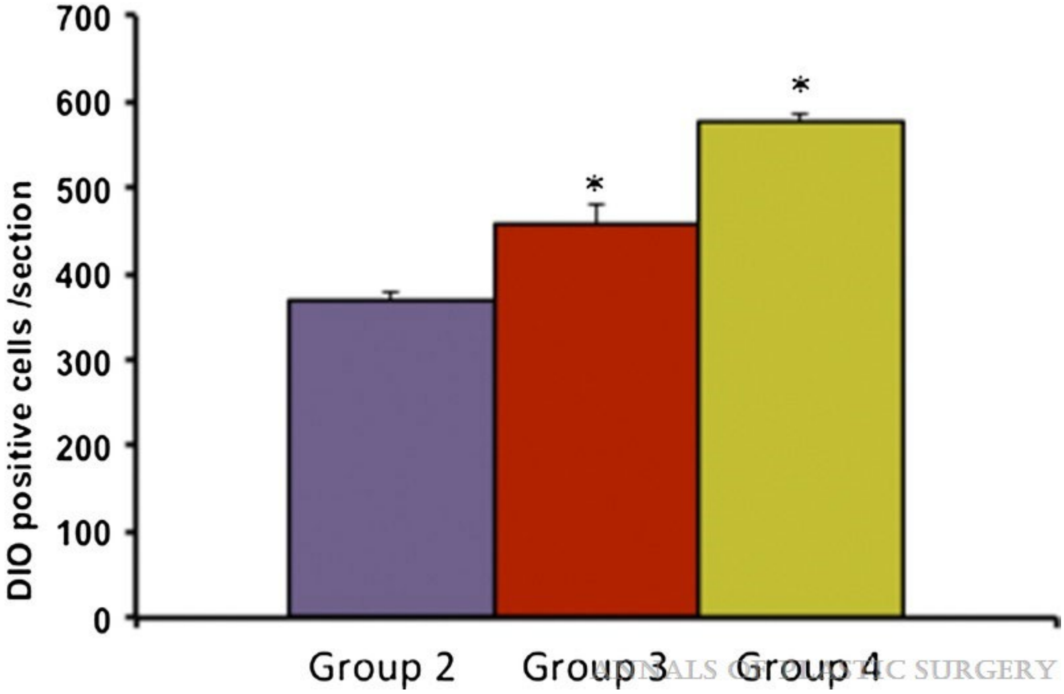

FIGURE 6

Comparison of the mean values of cells retained in the flap based on densitometry analysis (in arbitrary units) between the detection of green fluorescence emitted by the MSC-DIO and the blue fluorescence emitted by the cell nucleus immunostained with DAPI between groups where MSCs were injected.