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Surgical breast incisions treated with 2-octyl-cyanoacrylate *versus* intradermal nylon suture: a randomized clinical trial.

Incisões cirúrgicas mamárias tratadas com 2-octilcianoacrilato versus sutura intradérmica com fio de nylon: ensaio clínico randomizado.

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ABSTRACT

Objective: to evaluate the safety profile and aesthetic results of 2-octyl-cyanoacrylate *versus* intradermal nylon suture in breast surgeries. **Methods:** an open-label, randomized, clinical trial evaluating the occurrence of complications, such as dehiscence, hematoma, infection, and allergic reactions after the use of 2-octyl-cyanoacrylate or nylon thread. The size of the incisions, skin closure time, and total surgical time were also analyzed. The aesthetic outcome was evaluated at 40 and 180 days after surgery, by means of the average width of the surgical wound and by subjective conceptual assessment (optimal, good, reasonable, or poor). **Results:** 79 patients were included: 37 in the 2-octyl-cyanoacrylate group and 42 in the nylon suture group. The study was stopped before the end of patient recruitment due to the occurrence of a greater number of dehiscences in the adhesive group (OR: 11.42; 95%CI: 1.36-96.02; p=0.007). Regarding the other analyzed complications, the surgical duration and postoperative aesthetic result, no significant differences were observed between the groups. The mean operative wound size was greater in the adhesive group than in the suture group, but there was no correlation between wound size and the largest number of dehiscences. **Conclusion:** while the cosmetic outcomes with the two techniques were similar, there was a greater risk of dehiscence with the use of 2-octyl-cyanoacrylate compared to intradermal suturing.

Keywords: Cyanoacrylates. Breast. Tissue Adhesives. Sutures. Breast Neoplasms.

INTRODUCTION

Thousands of people are submitted to breast surgeries annually and surgical wound management should provide adequate functional and aesthetic repair. For this, the evolution of skin synthesis techniques has been fundamental to obtain better results[1-7]. Suturing with needle and thread is still the most commonly used method for surgical wound closure, because it is safe and effective[3,5,7,8]. These threads, which should generally be removed in the postoperative period, may favor the development of skin infections, and suturing may require a long learning curve[9,10].

The development of tissue adhesives was described in the 1950s as an alternative method for wound closure[4,11]. Among their advantages, we highlight the practicality of their execution and the fact that there is no need to return for the removal of the wound closure materials used[4,6]. Their use has been widespread through emergency procedures, especially in facial lesions and pediatric patients, with subsequent consolidation in elective procedures[6,12,13]. The aesthetic results, however, are controversial and local complications have also been described, including a greater possibility of dehiscence when compared to traditional sutures[4,6,13-17].

Given the above, this study aimed to compare the safety parameters between 2-octyl-cyanoacrylate (OCA) tissue adhesive and conventional nylon suture. The secondary objective was to evaluate the aesthetic results at 40 and 180 days after surgery.

METHODS

Phase IIb, open-label, randomized, clinical trial conducted at Clinic Hospital of Federal University of Goias (HC-UFG). Primary outcomes included four safety parameters: dehiscence, hematoma, allergy, and surgical site infection.

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Our secondary outcome was the aesthetic evaluation of the surgical scar at 40 and 180 days after the procedure.

The sample size calculation was performed considering a statistical power of 90% in the one-tailed test, with prefixed p-value of 0.05 and detection of 10% incidence of surgical wound dehiscences, including the possibility of 10% loss to follow-up for the aesthetic analysis. Thus, we calculated a total of 143 patients, randomly distributed in the two studied groups, as necessary for primary objective assessment. The detection of 10% incidence of surgical wound dehiscences was higher than the incidences found in different studies described in literature[18,19]. However, as this is a clinical trial aiming at evaluating the safety and effectiveness of the studied method, we adopted this value for the purpose of sample calculation.

The study included patients with benign or low-risk breast lesions with surgical indication. Exclusion criteria were diabetes *mellitus*, sensitivity to 2-octyl-cyanoacrylate, and previous history of keloids or hypertrophic scars.

The patients included in the study were divided by means of randomized raffle of previously sealed envelopes, all containing a printed card with the selected group (simple randomization). Randomization occurred before each surgical procedure and allocation confidentiality was respected during all phases of the process. The analyzed preoperative patient characteristics were gender, age, height, weight, hemoglobin dosage, leukocyte count, and body mass index.

Patients underwent exeresis of mammary tumor or quadrantectomy through an arciform skin incision. After removal of the surgical specimens, local hemostasis was reviewed by electrocoagulation. All patients received subdermal suture with separate stitches and internal knot, using 5.0 nylon thread, prior to the application of the techniques under comparison. This suture aimed at the uniform distribution of the tensile strength across the incision line, besides the alignment and slight surgical wound edge eversion. Prior to the use of 2-octyl-cyanoacrylate and intradermal suture performance, the skin was cleaned with 0.9% saline solution and carefully dried. Patients randomized to OCA had the adhesive applied over the incision, according to the technique described on the package leaflet, in three covers. For the nylon suture group, continuous intradermal suture with 4.0 nylon thread was performed.

We measured the total surgical time in minutes and the surgical wound closure time in seconds, including the subdermal closure, skin cleansing, and application of synthesis material. In OCA group, the time count was completed at the end of the polymerization of the third layer of adhesive applied over the wound. The sizes of the incision and excised lesion were measured in millimeters.

Patients in both groups were instructed regarding postoperative care, with emphasis on the orientation of waiting 24 hours for the first bath and hygiene care in the manipulated area. For OCA group, it was also advised not to remove the polymer formed after its application.

Patients were clinically evaluated at seven, 40, and 180 days after surgery. All patients received an instruction card with return dates and other relevant pieces of information. In the seven-day consultation, safety parameters were evaluated, such as the occurrence of dehiscence, surgical site infection, allergy, and hematoma formation.

At 40 and 180 days after surgery, the aesthetic aspect of the scar was recorded according to the examiner's subjective assessment, being "poor" when the scar was large and hypertrophic; "reasonable" when it was large or hypertrophic; "good", when thin and flat; and "optimal", when barely noticeable. The width of the scar (transverse distance, in millimeters, between the edges of the scar) was measured with standardized caliper. Follow-up appointments were performed by a single surgeon of the staff.

This study was approved by the Research Ethics Committee (protocol n# 014/05) and was conducted in accordance with the current principles of the Declaration of Helsinki. All participants were volunteers and signed an informed consent form prior to inclusion in the study.

Statistical analyses were performed with the aid of Statistical Package for the Social Sciences (SPSS version 19.0 for Windows). Numerical variables of normal distribution were compared by Student's t-test. The other variables were evaluated through contingency tables, using Chi-square method. Values of $p<0.05$ were considered significant.

RESULTS

An interim analysis of the study data was performed before its conclusion, given the perception of the largest number of dehiscences in OCA group. After conducting this analysis and confirming the significant increase in dehiscences in the adhesive group, the Safety Committee suggested immediate discontinuation of the study and communication of results to the research subjects. The interim analysis and the researchers' opinion were forwarded to the Research Ethics Committee of HC-UFG.

Thus, of the 143 patients previously calculated for inclusion in the study, only 79 were randomized due to the interruption of recruitment for safety reasons. Of these, 37 were allocated to OCA group and 42 to the nylon suture group. In OCA group, one female patient did not receive the randomized intervention due to hemorrhage requiring tubular drain insertion and interrupted stitch technique (Figure 1).

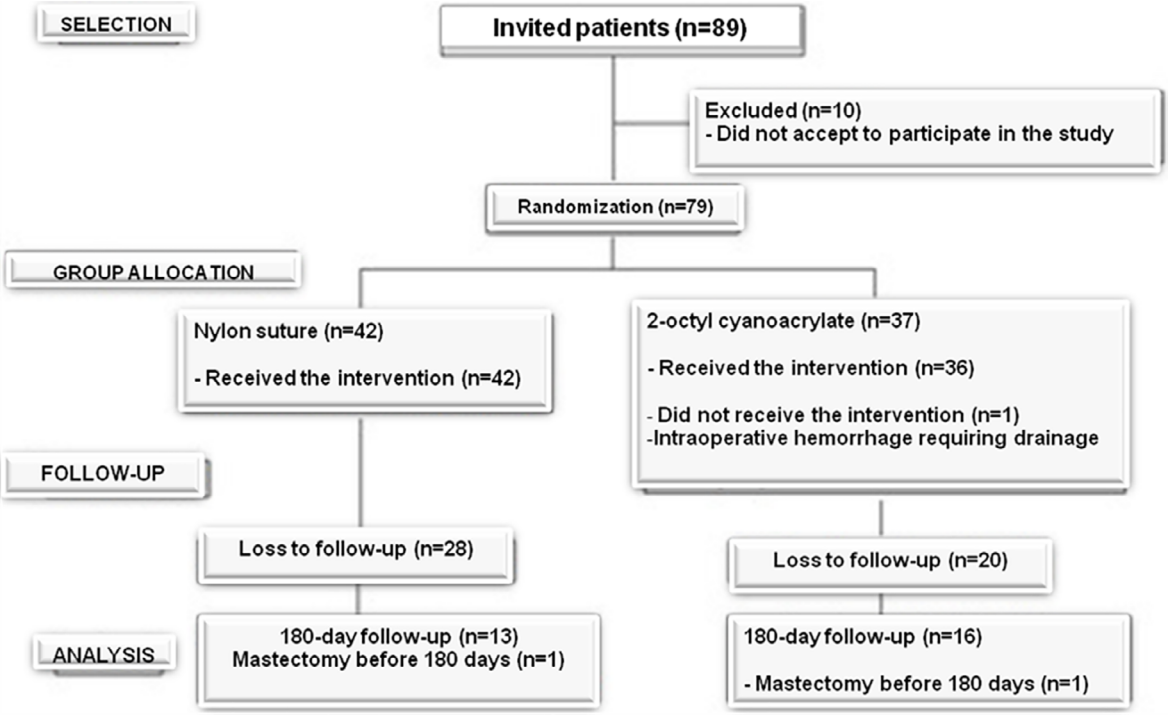

Figure 1. *Flowchart of recruitment, randomization, follow-up, and analysis of study participants.*

Among demographic characteristics, there was no significant difference between the analyzed groups, with 78 women and one man undergoing the study (Table 1). Seventy-eight patients underwent exeresis of mammary nodes or microcalcifications and one female patient underwent quadrantectomy. Surgical time, skin closure time, and lesion size did not show statistical difference between groups (Table 1). The mean incision size was larger in OCA group (32.97mm ± 10.54mm) compared to the nylon suture group (27.64mm ± 9.56 mm) (p=0.022).

Sixty-nine patients (87.34%) returned to the seven-day consultation, when the occurrence of dehiscence, hematoma, allergy, and surgical site infection was evaluated. There was an increase in the occurrence of dehiscence in OCA group in relation to the nylon suture group (RR=11.42; 95%CI: 1.36-96.02; p-value=0.007). There was no statistically significant difference between groups regarding infection occurrence (1 *versus* 1; RR=0.97; 95%CI: 0.06-16.17; p-value=0.983) or hematoma (3 *versus* 4; RR=0.70; 95%CI: 0.14-3.4; p-value=0.660). No allergic reaction occurred in any of the evaluated patients.

In no case there was total dehiscence of the surgical wound. In OCA group, there were three cases of dehiscence <1cm and six cases of size ≥1cm. In the nylon suture group, there was only one case of dehiscence, which was smaller than 1cm. All cases of partial dehiscence evolved with complete clinical resolution on subsequent evaluations. Considering the intention-to-treat data regarding the occurrence of dehiscence in OCA group, the number needed to harm was of 4.5.

The 40-day consultation aimed to evaluate the partial aesthetic result, and had the return of 39 patients (49.36%). There was no statistically significant difference between the subjective evaluation data and neither the average surgical scar thickness (Table 2). Similarly, with the follow-up of 29 patients (36.71%), no differences were observed in the 180-day evaluation (Table 3). Two patients (one from OCA group and one from the nylon suture group) were excluded at this stage of the study because they were diagnosed with breast cancer, undergoing a new surgical procedure between the 40-day consultation and the 180-day consultation, not permitting the late evaluation of the scar.

Table 1. *Population characteristics and surgical parameters of OCA and nylon suture groups.*

	OCA* group Average (±DP#)	NST** group Average (±DP#)	p
Age (years)	35.48 (12.76)	32.30 (12.84)	0.274
Total leukocytes (per µl)	6479.09 (2197.33)	6282.61 (1887.91)	0.749
Hemoglobin (g/dl)	12.83 (1.20)	12.85 (1.02)	0.951
Body mass index (kg/m^2)	22.97 (4.07)	23.63 (4.82)	0.546
Mean surgical time (min)	43.03 (22.54)	41.92 (19.85)	0.824
Skin closure time (sec)	557.51 (357.12)	582.98 (237.45)	0.707
Lesion size (mm)	23.65 (17.88)	22.06 (10.19)	0.638
Incision size (mm)	32.97 (10.54)	27.64 (9.56)	0.022

** OCA: 2-octyl-cyanoacrylate; ** NST: nylon suture technique; #: standard deviation.*

Table 2. *Average width of the surgical wound and subjective aspect of the aesthetic result at 40 days after surgery.*

	NST** group (n=22) Average (±DP#)	NST** group (n=17) Average (±DP#)	p
Average width (mm)	2.02 (1.65)	1.75 (1.54)	0.618***
Aspect			
Poor	2 (9.09)	3 (17.65)	0.746+
Reasonable	5 (22.73)	2 (11.77)	0.746+
Good	7 (31.82)	6 (35.29)	0.746+
Optimal	8 (36.36)	6 (35.29)	0.746+

** OCA: 2-octyl-cyanoacrylate; ** NST: nylon suture technique; #: standard deviation; ***: Student's t-test; +: Chi-square; p<0.05.*

Table 3. *Average width of the surgical wound and subjective aspect of the aesthetic result at 180 days after surgery.*

	OCA* group (n=16) Average (±DP#)	NST** group (n=13) Average (±DP#)	p
Average width (mm)	1.76 (1.77)	1.94 (2.39)	0.814***
Aspect			
Poor	1 (6.25)	1 (7.69)	0.617+
Reasonable	3 (18.75)	2 (15.38)	0.617+
Good	9 (56.25)	5 (38.46)	0.617+
Optimal	3 (18.75)	5 (38.46)	0.617+

** OCA: 2-octyl-cyanoacrylate; ** NST: nylon suture technique; #: standard deviation; ***: Student's t-test; +: Chi-square; p<0.05.*

DISCUSSION

The absence of significant difference between skin closure times was due to the strict observance of the product application norms, according to its package leaflet. Three layers of adhesive were applied 30 seconds apart between each application, and the interruption of the counting was performed only with the complete polymerization of the third layer. Although the average incision size in OCA group was significantly greater than in the nylon suture group, the time between the subdermal suture and the completion of skin synthesis was similar between the two groups. According to literature, the closure time with the use of the adhesive should have been shorter if the size of the incisions had been similar[6,15].

The higher occurrence of dehiscence with the use of OCA in relation to thread suture has already been reported by several authors[4,18]. In a recent meta-analysis, the risk of dehiscence with the use of adhesives has been three times higher than the risk of conventional suture[6]. However, the number of dehiscences observed in the present study was higher than the one commonly described in literature[6,19]. Possible explanations include the high skin moisture content and excessive sweating due to a physiological response to the tropical climate observed in central Brazil. These factors could accelerate the detachment of the polymer from the wound surface. Still, the habit of repeated baths could interfere with the initial healing process, although all patients were advised about the local care protocol.

The higher occurrence of dehiscence may also be justified due to cyanoacrylate histotoxicity. It is manifested by cell damage in vitro and inflammatory reactions in vivo, being attributed to the release of formaldehyde and acetate as degradation products[18,20-22]. Another relevant factor is the rigid structure and lack of elasticity after administration[23]. Even with all recommendations, it is impossible to avoid some degree of breast mobility. In this context, the next generation of tissue adhesives will need to combine chemical and physical processes to achieve high adhesion energy on various wet and dynamic surfaces[24].

Inadequate use of OCA did not seem to be a causal factor, since the surgical team had already mastery of the technique, including the publication of satisfactory results in an experimental study in rats[20]. However, the issue is controversial, and Gennari *et al*.[13] have concluded their study by mentioning that OCA has been effective and reliable in skin closure for breast surgery, yielding similar results to standard suture.

From the methodological point of view, the study has limitations for the evaluation of aesthetic parameters. The impossibility of reaching the previously calculated sample number and the follow-up losses in the 180-day evaluation made it difficult to compare the aesthetic result between the two groups. The researchers found it difficult to maintain participants' adherence, especially after 40 days. This was probably due to the availability of anatomopathological results of negative surgical specimens for malignancy in this period, as well as the absence of significant postoperative complications.

In addition, the 180-day follow-up is relatively short for aesthetic evaluation, as there is the possibility of decreasing differences between methods in longer evaluation periods[25]. However, there is description in literature of 90-day intervals as an acceptable time for aesthetic evaluation in the study of adhesives[26]. The determination of the 180-day period as late evaluation considers the difficulty of follow-up for longer periods in a Brazilian public health unit. It is observed, also as a limitation of the study, the use of subjective parameters for the aesthetic analysis. Therefore, our findings of the absence of aesthetic difference between the two groups should be carefully evaluated and analyzed in light of other comparative studies that also support the equivalence between the two methods from the cosmetic point of view[4,6,13-15].

It is noteworthy, as a positive point, that the analysis of the studied safety parameters (such as the occurrence of dehiscence, operative time, skin closure time, and mean size of incisions and lesions, for example) showed no impairment due to follow-up loss, since the parameters obtained in the operating room originated from all randomized patients and the occurrence of complications was evaluated in 87.3% of the sample.

Concluding, we observed in the present study that the use of 2-octyl-cyanoacrylate for closure of mammary surgical incisions increased the risk of dehiscence in relation to intradermal nylon thread suture. Therefore, considering the costs and risk profile, its use should be avoided in these surgeries. However, the cosmetic result of the scars was similar in both groups.

R E S U M O

Objetivo: *avaliar o perfil de segurança e os resultados estéticos do 2-octilcianoacrilato versus sutura intradérmica com fio de nylon em cirurgias mamárias.* **Métodos:** *ensaio clínico randomizado, aberto, que avaliou a ocorrência de complicações, como deiscência, hematoma, infecção e reações alérgicas após o uso do 2-octilcianoacrilato ou do fio de nylon. Também foi analisado o tamanho das incisões, o tempo de fechamento da pele e o tempo cirúrgico total. O resultado estético foi avaliado após 40 e 180 dias da cirurgia, por meio da largura média da ferida operatória e por avaliação subjetiva conceitual (ótimo, bom, razoável ou ruim).* **Resultados:** *foram incluídas 79 pacientes, sendo 37 no grupo 2-octilcianoacrilato e 42 no grupo de sutura com fio de nylon. O estudo foi interrompido antes do término do recrutamento dos pacientes pela ocorrência de maior número de deiscências no grupo do adesivo (OR: 11,42; IC95%: 1,36-96,02; p=0,007). Em relação às demais complicações analisadas, ao tempo cirúrgico e ao resultado estético no pós-operatório, não se observaram diferenças significativas entre os grupos. A média do tamanho da ferida operatória foi maior no grupo do adesivo em relação ao grupo da sutura, mas não houve correlação entre o tamanho da ferida e o maior número de deiscências.* **Conclusão:** *o 2-octilcianoacrilato apresentou maior risco de deiscência em relação à sutura intradérmica, com resultados estéticos equivalentes.*

Descritores: *Cianoacrilatos. Mama. Adesivos Teciduais. Suturas. Neoplasias da Mama.*

REFERENCES

1. Kummerow KL, Du L, Penson DF, Shyr Y, Hooks MA. Nationwide trends in mastectomy for early-stage breast cancer. JAMA Surg. 2015;150(1):9-16.
2. Freitas R Jr, Siqueira LB, Carrijo EN, Lacerda RP, Paulinelli RR, Rahal RM, et al. Temporal variation of breast cancer surgical treatment in a university hospital in Brazil's Central West region. Rev Col Bras Cir. 2013;40(3):180-5.
3. Paulinelli RR, de Oliveira VM, Bagnoli F, Chade MC, Alves KL, Freitas-Junior R. Oncoplastic mammaplasty with geometric compensation--a technique for breast conservation. J Surg Oncol. 2014;110(8):912-8.
4. Coulthard P, Esposito M, Worthington HV, van der Elst M, van Waes OJ, Darcey J. Tissue adhesives for closure of surgical incisions. Cochrane Database Syst Rev. 2010;(5):CD004287.
5. Harati K, Kolbenschlag J, Behr B, Goertz O, Hirsch T, Kapalschinski N, et al. Thoracic wall reconstruction after tumor resection. Front Oncol. 2015;5:247.
6. Dumville JC, Coulthard P, Worthington HV, Riley P, Patel N, Darcey J, et al. Tissue adhesives for closure of surgical incisions. Cochrane Database Syst Rev. 2014;(11):CD004287.
7. Gurusamy KS, Toon CD, Allen VB, Davidson BR. Continuous versus interrupted skin sutures for non-obstetric surgery. Cochrane Database Syst Rev. 2014;(2):CD010365.
8. Mackeen AD, Schuster M, Berghella V. Suture versus staples for skin closure after cesarean: a metaanalysis. Am J Obstet Gynecol. 2015;212(5):621.e1-10.
9. Steingrimsson S, Thimour-Bergström L, Roman-Emanuel C, Scherstén H, Friberg Ö, Gudbjartsson T, et al. Triclosan-coated sutures and sternal wound infections: a prospective randomized clinical trial. Eur J Clin Microbiol Infect Dis. 2015;34(12):2331-8.
10. Rufai SR, Holland LC, Dimovska EO, Bing Chuo C, Tilley S, Ellis H. A National Survey of Undergraduate Suture and Local Anesthetic Training in the United Kingdom. J Surg Educ. 2016;73(2):181-4.
11. Coover, NH, Joyner FB, Sheere NH, Wicker TH. Chemistry and performance of cyanoacrylate adhesive. Special Tech Papers. 1959;5:413-7.
12. Singer AJ, Kinariwala M, Lirov R, Thode HC Jr. Patterns of use of topical skin adhesives in the emergency department. Acad Emerg Med. 2010;17(6):670-2.
13. Gennari R, Rotmensz N, Ballardini B, Scevola S, Perego E, Zanini V, et al. A prospective, randomized, controlled trial of tissue adhesive (2-octylcyanoacrylate) versus standard wound closure in breast surgery. Surgery. 2004;136(3):93-9.
14. Brown JK, Campbell BT, Drongowski RA, Alderman AK, Geiger JD, Teitelbaum DH, et al. A prospective, randomized comparison of skin adhesive and subcuticular suture for closure of pediatric hernia incisions: cost and cosmetic considerations. J Pediatr Surg. 2009;44(7):1418-22.
15. Scott GR, Carson CL, Borah GL. Dermabond skin closures for bilateral reduction mammaplasties: a review of 255 consecutive cases. Plast Reconstr Surg. 2007;120(6):1460-5.

16. Min JY, Jang YJ. Use of 2-octyl-cyanoacrylate (dermabond) tissue adhesive for tip graft fixation in open rhinoplasty. Otolaryngol Head Neck Surg. 2011;145(5):737-41.
17. Bowen C, Bidinger J, Hivnor C, Hoover A, Henning JS. Allergic contact dermatitis to 2-octyl cyanoacrylate. Cutis. 2014;94(4):183-6.
18. Singer AJ, Thode HC Jr. A review of literature on cyanoacrylate tissue adhesive. Am J Surg. 2004;187(2):238-48.
19. Piper ML, Esserman LJ, Sbitany H, Peled AW. Outcomes following oncoplastic reduction mammoplasty: a systematic review. Ann Plast Surg. 2016;76 Suppl 3:S222-6.
20. Freitas-Junior R, Paulinelli RR, Rahal RM, Moreira MA, Oliveira EL, Aiko KF, et al. The use of 2-octyl cyanoacrylate or nylon suture for skin closure produces similar modifications in scar tissue (an animal model). J Plast Reconstr Aesthet Surg. 2008;61(8):990-2.
21. Souza SC, Briglia CH. Comparative study of the use of ethyl cyanoacrylate adhesive and intracutaneous suture for cutaneous excision closure. Rev Bras Cir Plast. 2011;26(4):566-72.
22. Montanaro L, Arciola CR, Cenni E, Ciapetti G, Savioli S, Filippini F, et al. Cytotoxicity, blood compatibility and antimicrobial activity of two cyanoacrylate glues for surgical use. Biomaterials. 2001;22(1):59-66.
23. Kelmansky R, McAlvin BJ, Nyska A, Dohlman JC, Chiang HH, Hashimoto M, et al. Strong tissue glue with tunable elasticity. Acta Biomater. 2017;53:93-9.
24. Li J, Celiz AD, Yang J, Yang Q, Wamala I, Whyte W, et al. Tough adhesives for diverse wet surfaces. Science. 2017;357(6349):378-81.
25. Nipschagen MD, Hage JJ, Beekman WH. Use of 2-octyl-cyanoacrilate skin adhesive (Dermabond) for wound closure following reduction mammaplasty: a prospective, randomized intervention study. Plast Recontr Surg. 2008;122(1):10-8.
26. Singer AJ, Thode HC Jr, Hollander JE. Research fundamentals: selection and development of clinical outcome measures. Acad Emerg Med. 2000;7(4):397-401.

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