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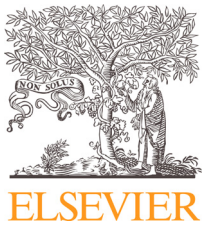

Reduction of seroma and improvement of quality of life after early drain removal in immediate breast reconstruction with tissue expander. Preliminary report from a randomized controlled study

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Summary Seroma is the most common complication of breast reconstruction with tissue expander (incidence 0.2-20%) with increased risk of infection and implant loss by 4-6 fold. About 90% of plastic surgeons routinely placed drains for its prevention. We theorized that early drain removal is a safe procedure that improves postoperative quality of life (QoL), reducing pain, length of hospital stay, and limitations on daily activities. We divided 49 patients operated on between September 2016 and March 2018 (follow-up: 9-26 months) into two groups: Group1 (output-based; drains removed when <30 ml/day); and Group2 (early-removal; at 3-4 days postop.). A study-specific questionnaire about the patient's QoL was conducted 3 weeks after surgery. We performed an intention-to-treat analysis. A comparison was performed using a Fisher test and a Mann-Whitney U test with $p = 0.05$. We observed lower production of wound fluid (641±49 ml vs 231±20 ml; $p = 0.004$), and a shorter time until wound healing (31.3±4.2 days vs 22±3.9 days; $p = 0.031$) for Group 2. The difference for infection ($p = 0.36$), impaired wound healing ($p = 0.22$), and the seroma formation period ($p = 0.11$) was not significant. Group 2 experienced less breast pain (8% vs 87.5%; $p = 0.001$), fewer limitations in daily activities (16% vs 50%; $p = 0.002$), in mobility (20% vs 83.3%; $p = 0.001$), and in social life (8% vs 91.7%; $p < 0.001$), and a better quality of sleep than Group 1 (36% vs 75%; $p = 0.002$). Group 2 did not

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require home care after hospital discharge ($p < 0.001$). The limitations of study are: its small sample size, the wound healing assessment, and the use of a non-validated questionnaire.

Introduction

The American Society of Plastic Surgeons (ASPS) reported 101,657 breast reconstructions in 2018, nationwide, of which 69,921 with expander/implant position.[1]

Seroma is the collection of serous fluid in dead space beneath a wound that may need aspiration. It is one of the most common complications following breast reconstruction with an expander, coming in at an incidence that varies between 0.2% and 20%.[2]

Several factors are implicated: large and irregular dead space after mastectomy, insertion of a foreign body (expander, prosthesis, and ADM), the extent of lymph node dissection, obesity, movement of the chest wall, and adjuvant radiotherapy (RT).[2]

However, the pathophysiology continues to be debatable: seroma is a mixture of a collection of lymph and acute inflammatory exudate. In breast reconstruction, there are three etiologic factors for local inflammation that can lead to seroma: 1) Surgical trauma (non-viable tissue, lymphatic disruption, and electrocautery damage); 2) A local "hypovascular" state; and 3) Foreign body reaction (tissue expander/ADM).[3-5]

Seroma can lead to complications such as infection, delayed wound healing, dehiscence, a prolonged hospital stay, loss of the implant, a need for secondary surgery, and delayed adjuvant therapy, with a consequent increase in global costs.[3,6,7-11]

There are only a few studies that evaluate the potential risk and cost of complications in breast reconstruction. In a study of Gabriel et al., there was hypothesized a mean cost for complication of $10,402.[12] This value was confirmed also by Smith et al.[13] Same results are described by Damen that estimated about €12,400 the costs for short-term complications of tissue expander breast reconstruction.[14] Tran et al. in a literature review calculated the cost of possible complications; in particular for aspiration of seroma, they calculated a cost of $370.87.[15] So, the expected cost (probability of complication * actual cost) of seroma was calculated in $846.24. Incorporating global complication data (seroma, skin necrosis, IV antibiotics, and implant removal) from published literature resulted in the excess cost of about $14,000 (increase of 5% from the cost of a successful reconstruction).[15]

In breast reconstruction with tissue expanders, about 80–90% of plastic surgeons routinely put in closed-suction drainage to avoid postoperative hematoma or seroma.[6,16]

Drain removal policies vary widely across Breast Cancer Centers.

In today's literature, most studies report drain removal when volumes are <20–50 ml/24 h, although this policy necessitates patients going home with drains or undergoing long hospital stays.[2,16-25]

However, drain permanence is associated with healthcare costs, discomfort for patients, and daily home nursing.[26]

In fact, most studies report that the patients with drains tend to have longer lengths of hospital stay with higher cost. Reducing drain use decreases costs and outpatient attendances; this strategy does not prolong the time for seroma resolution and it is tolerable for the patients.[27-30]

Therefore, the goal of our randomized controlled trial was to compare early drain removal with output-based drain removal in patients who underwent mastectomy and immediate reconstruction with a tissue expander. Our experimental hypothesis was to demonstrate that early drain removal is a safe procedure that improves clinical outcomes and QoL. The mechanism of action underlying our proposed approach was threefold, given that early drain removal makes it possible to: 1) Avoid continuous seroma development caused by active drain suction (stopping the circle of "the drain itself potentially perpetuating drainage"); 2) Reduce the risks associated with a "foreign body reaction" through tissue inflammation and infection; and 3) Improve QoL by reducing pain, the length of hospital stay, and limitations on daily activities.

Patients and methods

In a randomized controlled trial, the Authors collected the data of 124 consecutive patients who underwent mastectomy and breast reconstruction at the multidisciplinary Breast Unit in Ospedali Riuniti OORR, Foggia, Italy between September 2016 and March 2018. We included patients older than 18 years for whom it was planned to perform skin nipple sparing(SNS) or skin sparing (SS) mastectomy for breast cancer and immediate positioning of a breast expander (without mesh) including placement of a suction drain, regardless of TNM classification. The patients were allocated under a restricted randomization method using sealed envelopes that were prepared prior to the study's start. Subsequently, after allocation the patients were blinded to interventions. The exclusion criteria were skin-reducing mastectomy, reconstruction with flap, direct-to-implant reconstruction (with or without mesh or ADM), and axillary dissection.

The study protocol was approved by the Local Medical Ethics Committee in accordance with the Helsinki Declaration of 1975, as amended in 2008. Informed consent was obtained from all patients for inclusion in the study. Moreover, the clinical trial was registered under identifier number NCT04188821 (ClinicalTrials.gov).

Pursuant to CONSORT guidelines, the Authors defined two groups prior to the study: in Group 1, the "output-based group," we removed drains when the suction drain flow

was less than 30 ml/day for at least 2 days with no further signs of infection, fluid collection or impaired wound healing ("complicated," see below). Ultimately, we removed drains 3 weeks postoperatively (21 days postop.) even if the flow was higher than 30 ml/day. However, leakage or severe patient discomfort could lead to immediate drain removal at any time during postoperative care, as per our standard breast drain protocol.

In Group 2, referred to as the "early-removal group," we removed the drains on hospital discharge, 3-4 days after surgery, regardless of output at that time. Nevertheless, some patients in this group were excluded postoperatively if early drain removal on hospital discharge was not feasible or not considered safe by the surgeon, for example, due to infection or impaired wound healing.

All mastectomies and subpectoral pockets were performed using an ultrasonic scalpel (Focus Ultracision Harmonic Scalpel® ETHICON); a single drain was applied in the pre-pectoral area (Blake silicon flat drain® 19G, ETHICON), and the wounds were closed intradermally. We implanted the tissue expander without mesh (Mentor® CPX™ 4, style 8100 low height -8200 medium height -8300 tall height; from 250 cc to 550 cc volume size) in a sub-pectoral pocket, and we used cefazolin as a short-term prophylaxis (no postoperative outpatient antibiotics). All patients were allowed to leave the hospital 3-4 days after surgery, and had a weekly wound care appointment after hospital discharge.

In consequence, all patients were followed from the day before surgery until wound healing. In particular, we defined wound appearance by observing the characteristics of its borders (adherent or dehiscent) and the presence or otherwise of signs of infection. We then classified wound healing as "normal" if there weren't any problems, "complicated" if we observed infection and/or dehiscence, and "complete" if a scar formed. This method for wound healing assessment was qualitative and based on the Surgeon's experience, which means that it is not a standardized method and therefore may be considered a limitation of this study.

Home care was not required in the case of hospital discharge without drains; moreover, in cases where seroma collected, management consists of US-guided aspiration.

The primary endpoint of this study was the clinical safety of early drain removal.

The Authors selected five clinical variables to determine the safety of early drain removal: the incidence of wound infection (defined as the appearance of local signs/symptoms, such as erythema, edema, induration, increased pain, and a change in drainage to a purulent nature and fever) confirmed by swabs; complications in wound healing (defined as an unclosed wound 3 weeks postoperatively); the duration of seroma formation (the period that a drain or seroma aspiration is needed during days after surgery); total fluid volume (the sum of drain volumes and the volume of seroma aspirations if required); and the time until wound healing (in days after surgery).

The secondary endpoint of this study was the improvement of postoperative QoL.

A questionnaire about patient QoL was conducted postoperatively (three weeks after surgery, on the last day of draining feasible in situ). This timeframe was established to ensure that all patients could be included in post-drain removal QoL analysis.

However, no validated specific questionnaire on the role drains play on QoL exists in literature. We consequently designed a study-specific questionnaire based on drain-related problems, such as pain (using the *visual analog scale* (VAS) to measure intensity), discomfort, sleep disturbance, and repercussion on daily activities and social life.

An intention-to-treat (ITT) analysis was performed to ensure that every patient randomized to the clinical study was taken into account for the statistical analysis. In fact, we collected 124 patients; 75 were excluded for various reasons, and 49 were single-blinded randomized in two well-balanced groups. Six patients were excluded in follow-up for postoperative medical problems or for interference with protocol; in consequence, all of the 49 patients randomized and allocated to the groups were analyzed.

We present summary statistics as means with standard deviation (Std) and medians with a range for continuous variables, and as frequencies and percentages for categorical variables. The continuous data were assessed for normality of distribution using a Kolmogorov-Smirnov test that revealed a normal Gaussian distribution. Comparison of the two treatment groups was performed using a Fisher exact test for categorical variables, or a Mann-Whitney U test for continuous consequent variables. An expert bio-statistician performed the statistical analysis using Statistical Package for Social Sciences (SPSS version 16.0). A value of p less than 0.05 was considered statistically significant.

Results

Six out of 49 patients were excluded in follow-up: three in the output-based group and three in the early-removal group. In particular, four patients were excluded as a result of incorrect drain removal timing, and two patients for postoperative medical problems (Figure 1).

Clinical features of the 49 patients who were randomized were compared to ensure a well-balanced randomization (Table 1). Age, body mass index (BMI), American Society of Anesthesiologists (ASA) score, smoking, diabetes, type of surgery, and neoadjuvant therapy were compared, and no significant difference was noted.

The clinical variables analyzed to evaluate the clinical safety of early drain removal were reported in Table 2.

The Authors observed two significantly positive results for the early-removal group (Group 2): lower production of wound fluid measured as the sum of drain and aspiration volumes (641 ml $\pm$ 49 vs 231 ml $\pm$ 20, with $p = 0.004$), and a shorter time until wound healing (31.3 days $\pm$ 4.2 vs 22 days $\pm$ 3.9, with $p = 0.031$).

Nevertheless, there was no statistically significant difference for infection (1 case vs 0, $p = 0.36$), for impaired wound healing (2 cases vs 0, $p = 0.22$), and for the duration of seroma formation (24.7 days $\pm$ 9.3 vs 21.5 days $\pm$ 7.5, $p = 0.11$).

A statistically significant difference was noted for all six queries on the postoperative questionnaire, with a better score for the early-removal group (Table 3).

The Authors noted that the patients in the early-removal group experienced less breast pain ("no/a little pain" 8% vs 87.5%, "moderate" 84% vs 8.3%, "severe" 8% vs 4.2%; $p = 0.001$), fewer limitations in their daily activities ("no/a

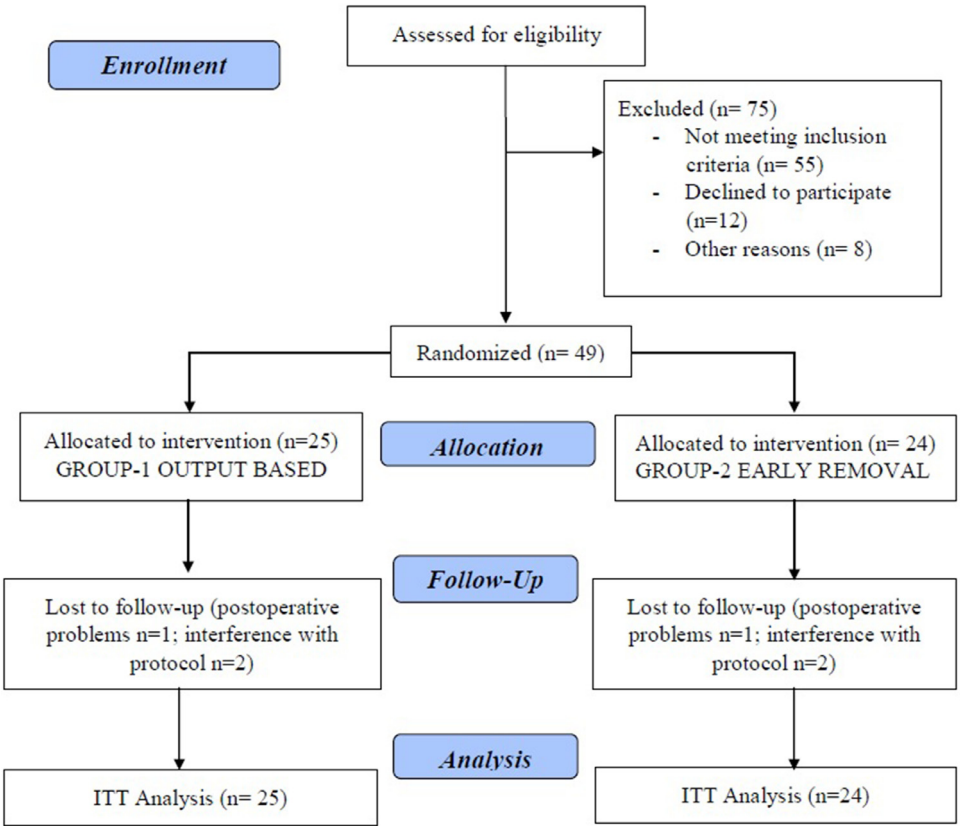

Fig. 1 Flow diagram of our randomized trial adhering to CONSORT guidelines.

Table 1 Clinical features of study population.

VARIABLE	GROUP 1 ($N=25$)	GROUP 2 ($N=24$)	p value
BMI			
MEAN(±STD)	25.3(±4.21)	26.2(±5.41)	0.224
MEDIAN (RANGE)	24.7 (18.1; 38.1)	25.3 (18.3; 38.6)	
AGE			
MEAN(±STD)	53.4(±10.8)	52.6(±18.9)	0.441
MEDIAN (RANGE)	51 (31; 74)	53 (32; 70)	
ASA SCORE			
1	14 (56%)	13 (54.2%)	
2	10 (40%)	11 (45.8%)	0.614
3	1 (4%)	0	
4	0	0	
SMOKING			
NO	16 (64%)	13 (54.2%)	0.084
YES	9 (36%)	11 (45.8%)	
DIABETES			
NO	23 (92%)	22 (91.7%)	0.878
YES	2 (8%)	2 (8.3%)	
TYPE OF SURGERY			
SNS (skin nipple sparing)	21 (84%)	22 (91.7%)	0.778
SS (skin sparing)	4 (16%)	2 (8.3%)	
NEOADJUVANT THERAPY			
NO	22 (88%)	23 (95.8%)	0.876
YES	3 (12%)	1 (4.2%)	

Table 2 Clinical variables analyzed.

VARIABLE	GROUP 1 ($N=25$)	GROUP 2 ($N=24$)	P value
DAYS WITH DRAINAGE			
MEAN (±STD)	9.7 (±5.4)	3.6 (±0.9)	NR
MEDIAN (RANGE)	9 (7; 21)	3.5 (3; 11)	
INFECTION			
NO	24 (96%)	24 (100%)	0.36
YES	1 (4%)	0	
COMPLICATED WOUND HEALING			
NO	23 (92%)	24 (100%)	0.22
YES	2 (8%)	0	
TIME UNTIL WOUND HEALING			
MEAN (±STD)	31.3(±4.2)	22(±3.9)	0.031
MEDIAN (RANGE)	35 (26; 54)	18 (16; 26)	
TOTAL FLUID VOLUME			
MEAN (±STD)	641.2(±49.8)	231.8(±20.2)	0.004
MEDIAN (RANGE)	590 (480; 950)	190 (120; 280)	
DAYS OF SEROMA FORMATION			
MEAN (±STD)	24.7 (±9.3)	21.5 (±7.5)	0.11
MEDIAN (RANGE)	20 (10; 38)	14 (6; 24)	

Tables 3 Patient related outcomes analyzed.

QUESTION	GROUP 1 ($N=25$)	GROUP 2 ($N=24$)	p value
1. DO YOU HAVE ANY PAIN AT BREAST SINCE SURGERY (use VAS scale for intensity) ?			
NO/A LITTLE (0-3)	2 (8%)	21 (87.5%)	
YES, MODERATE (4-6)	21 (84%)	2 (8.3%)	0.001
YES, SEVERE (7-10)	2 (8%)	1 (4.2%)	
2. DO YOU HAVE ANY LIMITATIONS IN PERSONAL CARE OR DAILY ACTIVITIES?			
NO/A LITTLE	4 (16%)	12(50%)	
YES, MODERATE	13 (52%)	11(45.8%)	0.002
YES, SEVERE	8 (32%)	1 (4.2%)	
3. DO YOU NEED HOME CARE SINCE SURGERY?			
NO	2 (8%)	24 (100%)	<0.001
YES	23 (92%)	0	
4. DO YOU HAVE ANY DISTURBANCE IN QUALITY OF SLEEP?			
NO	9 (36%)	18 (75%)	0.002
YES	16 (64%)	6 (25%)	
5. DO YOU HAVE ANY DISTURBANCE IN MOBILITY (WALKING, DRIVING)?			
NO	5 (20%)	20 (83.3%)	
YES, MODERATE	15 (60%)	4 (16.7%)	0.001
YES, SEVERE	5 (20%)	0	
6. DO YOU HAVE ANY LIMITATION IN SOCIAL LIFE?			
NO	2 (8%)	22 (91.7%)	
YES, MODERATE	18 (72%)	2 (8.3%)	<0.001
YES, SEVERE	5 (20%)	0	

little limitation" 16% vs 50%, "moderate" 52% vs 45.8%, "severe" 32% vs 4.2%; $p=0.002$), in mobility ("no/ limitation" 20% vs 83.3%, "moderate" 60% vs 16.7%, "severe" 20% vs 0%; $p=0.001$), and in social life ("no" 8% vs 91.7%, "moderate" 72% vs 8.3%, "severe" 20% vs 0%;$p<0.001$), and a better quality of sleep than patients in the output-based group ("no disturbance" 36% vs 75%, $p=0.002$). Furthermore, the early-removal group did not require home care after hospital discharge ($p<0.001$).

Discussion

Seroma is one of the most common complications following breast reconstruction with a tissue expander, for which closed-suction drains are routinely placed for prevention.[31] Time-to-drain removal is an area of debate because it can affect hospital stay duration, number of outpatient visits, costs and patient QoL.[7,18]

Higher drainage volume means a longer duration of drains and disrupts patients' postoperative life. In general, as long as drains remain in position, antibiotics are administered and normal daily activities such as showering are restricted.[16] Furthermore, some studies indicate that longer drainage time is a risk factor for surgical site infection and expander loss, because drains can create a direct communication between the mastectomy pocket and the outside environment.[8-10,32]

In fact, seroma and eventual infection require additional treatments (intravenous (IV) antibiotic therapy and/or surgical revision), delaying adjuvant therapy and potentially ultimately leading to implant loss.[11]

These factors suggest minimizing the number and duration of drains placed after expander-based breast reconstruction.[8-10]

In a review of 4669 members of the ASPS and the Canadian Society of Plastic Surgeons, more than 93% of participants cited volume criteria for drain removal, and most frequently a drain output of <30 mL over 24 h (86%).[19] Phillips et al. also concluded that the majority (87%) of the plastic surgeons use the criteria of drainage volume ≤ 30 ml/24 h to remove the drains.[6] The theory behind removing drains based on daily volume probably came from the study by Tadych et al., who reported an association of drain output with seroma formation in post-mastectomy patients.[22] These Authors found that no significant seromas formed when the total 24-hour drainage was <20 mL. To limit the length of hospital stays, subsequent studies analyzed the duration of drains in situ.[33] In particular, Parikh et al., processing data from 100 mastectomies, did not find a statistically significant difference in either mean volumes of fluid, aspiration numbers or return visits for drain removal at 3 days vs 6 days.[34] Somers et al. in a prospective randomized trial on 108 patients find that there is no significant difference in mean number of aspirations and time to resolution of seromas for drain removal at first postoperative day vs when drainage was <30 mL/24 h.[35] Likewise, in a prospective study, Yii et al. did not find a significant difference in wound healing for drain removal at 48 h vs when drainage was <30 mL/24 h.[36] In his trial, Inwang et al., processing data from 84 patients, did not find significant difference in either mean number of aspirations required and wound complications, for drain removal on day 5 postoperative vs when drainage was less than 20 mL over 2 consecutive days.[37] Other studies reveal another problem for a prolonged drains in situ: a tendency to encourage seroma formation by stimulating an inflammatory exudate response.

Five studies published between 1999 and 2011 comparing early drain removal with volume-controlled drainage have demonstrated that volume-controlled drainage is superior, but increases the length of hospital stay or discharges with a drain.[23,24,26,38] On the other hand, Kelley and colleagues performed a systematic review of more than 790 patients and found no difference between early and late drain removal.[39] Moreover, Crosby et al. noted a 5% per day increased rate of overall complications in prolonged times for drain removal, while Mendenhall et al. found an indirect association between a drain duration of more than 20 days and tissue expander loss.[32,40]

Moreover, multiple studies have demonstrated that early drain removal does not result in increased seroma formation, infection or donor or recipient site complication.[7,34,36]

This study backs the fact that early drain removal is at least as effective as extended drain duration in the prevention of seroma and, additionally, that fewer drains can reduce patient discomfort and hospital length of stay.

In our study, we demonstrated that early drain removal was clinically safe, and that the total volumes of fluid drained and aspirated were significantly lower in the early-removal group.

Early drain removal makes it possible to avoid continuous seroma development caused by active drain suction, and reduces the risks associated with "foreign body reaction" such as tissue inflammation and infection.

Only one patient with a postoperative infection was in the output-based group, but this fact was not statistically significant.

Patients in the early-removal group scored significantly better on the postoperative QoL questions.

First, a significant difference was noticed regarding postoperative pain, with patients in the early-removal group suffering less. This difference could not be explained by the type of surgery and might, therefore, be related to the drain itself.

Second, a significant difference was observed regarding restrictions in daily activities and personal care, with patients in the output-based group experiencing more limitations in dressing, practicing sports, doing housework, and taking a shower or bath.

Significantly more patients in the output-based group felt limited in their daily activities because of the need for frequent wound care at home or at the hospital. This difference cannot be explained by the number of wound care appointments in hospital, since there was no significant difference in the number of these appointments for patients in either of the two groups. Moreover, several patients mentioned that they perceived in-hospital appointments to be part of the recovery process, and not as a major issue. This allows us to state that home care is the only relevant factor in this context.

Third, a significant difference was noted in patient mobility, with patients in the early-removal group feeling more mobile, especially through driving.

Finally, patients in the early-removal group felt significantly more limited in their social life. The presence of a drain kept people at home because of the visibility of the drains, limitation to movement, and coming into daily contact with their ailment.

The limitations in our study are: its small simple size, a method for assessing wound healing that is qualitative rather than standardized and based on the surgeon's experience, and the use of a non-validated questionnaire, though this is because a suitable validated alternative in the literature was not available. In spite of these limitations, the significant differences between both groups cannot be ignored, suggesting the clear repercussions of drain-related impact on seroma volume and QoL for patients who underwent a mastectomy and reconstruction with tissue expanders.

Conclusions

Our data suggest that it is clinically safe and preferable to remove drains early after breast cancer surgery. Better results were obtained for patients in the early-removal group, even when statistical significance was not obtained for each variable. Moreover, the potential improvement in QoL for patients with breast cancer has a significant value. We are consequently collecting and analyzing other data in order to expand this randomized controlled trial in future and produce a "stronger" study.

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