Clinical Trial of Chlorinated Polyethylene for Facial Prosthetics

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Purpose: Extraoral maxillofacial prostheses have been fabricated with silicone elastomer for 50 years with few improvements. The objective of this controlled, randomized, prospective, double-blind, single-crossover, multicenter, phase III clinical trial was to determine the noninferiority of chlorinated polyethylene elastomer (CPE) to silicone elastomer for fabricating prostheses. ***Materials and Methods:*** Forty-two patients were randomly assigned to wear a custom-made prosthesis fabricated from both materials for 4 months and asked to rate their satisfaction (0 = not satisfied, 10 = completely satisfied). Many other measures of prosthesis performance were investigated (see online appendices). ***Results:*** Of the 28 patients who completed the study, 68% had used silicone prostheses previously. Overall, patients rated the silicone prosthesis higher than CPE (difference: 2.2, 95% confidence interval [CI]: 0.9 to 3.6, $P = .017$). Previous users had a stronger preference for silicone (difference: 3.3, 95% CI: 1.7 to 4.9, $P = .001$), while the 9 new users rated the two materials similarly (difference: 0.0, 95% CI: –2.1 to 2.1, $P = 1.00$). ***Conclusions:*** The noninferiority of CPE could not be established because of the early termination of the trial. Previous users of silicone prostheses preferred those made of silicone. However, new users expressed no preference between prostheses fabricated with the low-cost CPE or silicone. The authors have developed original clinical trial methodology for assessing extraoral maxillofacial prostheses. *Int J Prosthodont 2010;23:263–270.*

Patients with significant facial defects—usually a consequence of extensive surgery, congenital defects, or traumatic injuries—require complex prosthetic facial rehabilitation. Successful correction of such defects goes far beyond esthetic considerations. Prosthesis wearers are constantly reminded of their afflictions, profoundly affecting quality of life and debilitating them and their families emotionally.[1–3] Rigorous clinical trials are critical to determine the best facial reconstructive methods for this patient group.

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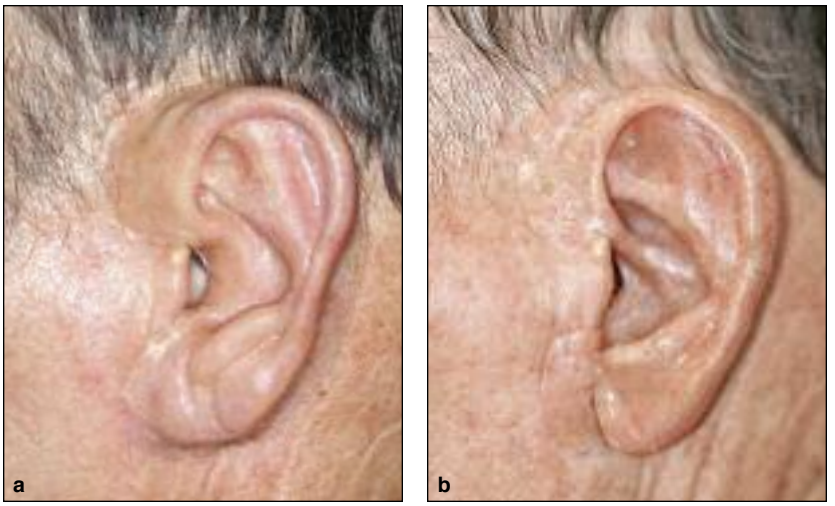

Fig 1 Comparison of **(a)** a total ear prosthesis made of silicone in 1999 with **(b)** one made in 2005 with thermoplastic CPE for the same patient. The prosthesis made from thermoplastic CPE was built-up in pigmented layers in a three-part gypsum/polymer mold with flocked overlay and heated at 115°C (240°F) at 69 kPa (0.7 bar, 12 psi) for 10 minutes (Fig 1a reprinted from Kiat-amnuay[23] with permission).

Extraoral maxillofacial prostheses (EMFPs) are artificial substitutes for missing biologic structures. EMFPs are the only option for many cancer and trauma patients. New and improved EMFP materials are needed.[4] Silicone elastomers have been used to make EMFPs for more than 50 years with few improvements.[5] Many patients are dissatisfied with the esthetics, color stability, retention, function, and longevity of their EMFPs,[4,6–14] and approximately 12% never wear them.[15] The high cost of medical-grade silicone elastomers ($400/kg) limits maxillofacial prosthetic services in developing countries and underserved populations in the United States.

Dow Chemical's chlorinated polyethylene elastomer (CPE; formerly CPE3614A, now Tyrin CM0136), an industrial-grade thermoplastic elastomer, may be a feasible substitute for silicone.[16,17] CPE fabrication was developed for EMFP patients beginning in 1978.[18] Because there is no curing chemistry, it is less toxic than thermosetting silicone materials[19] and noncarcinogenic.[16] It is less irritating to the mucosa than silicone and well tolerated by patients.[20,21] A previous phase II clinical trial suggested few differences between silicone and the less-expensive CPE (approximately $10/kg).[22] At the inception of this research, Silastic Adhesive A/MDX4-4210 with a polyurethane liner was considered the gold standard in the field with 41% popularity in 1992.[5] Addition-cured platinum silicone elastomers that were available in 2001 or 2002 were new to the market and not fully reported in the literature. Figure 1 shows an ear prosthesis made of silicone in 1999 and CPE in 2005, manufactured for the same patient (not included in this study).

The current study was a prospective, randomized, controlled, double-blind, single-crossover, multicenter, phase III clinical trial comparing EMFPs made of thermoplastic CPE and medical-grade silicone for *(1)* noninferiority of CPE based on outcome measures of functional and subjective characteristics, *(2)* noninferiority of patients' quality of life, and *(3)* prosthesis longevity.

Materials and Methods

Study Population

Patients were enrolled at the University of Texas M. D. Anderson Cancer Center, Houston, Texas, and the Odette Cancer Centre, Sunnybrook Health Sciences Centre, Ontario, Canada. Potential participants were recruited from each institution's clinic waiting list, new patients identified in the clinic, and patients referred by other health care providers. The institutional review board at each participating center approved the study protocol. Patients meeting the following inclusion criteria were enrolled:

- 21 years of age or older
- Required treatment for a developmental or acquired extraoral facial defect
- Had a fully healed wound (6 months postsurgery or radiation)
- Had a defect no larger than 9 × 12 cm
- Were sufficiently cognizant to answer questionnaires
- Agreed to wear the prosthesis for at least 6 hours per day
- Agreed to use the prescribed adhesive (Daro Adhesive Extra Strength B-200-ES, Factor II) and clean and store the prosthesis as instructed
- Planned to return to the research institution for a 10-month period
- Were able to manage the prosthesis themselves or with the help of a caregiver for a 10-month period
- Had a Karnofsky score ≥ 60[24]

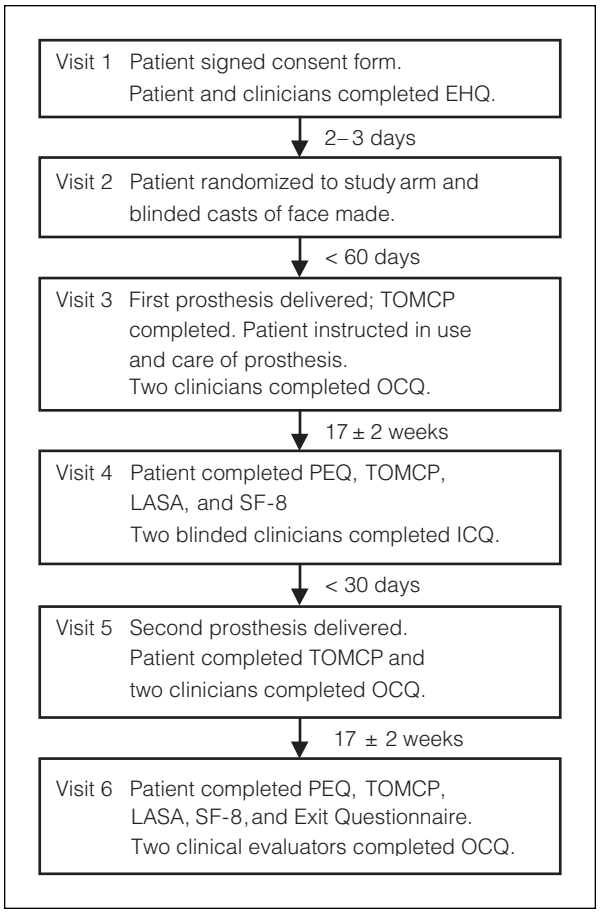

Fig 2 A flow diagram of patient visits. EHQ = Entry Health Questionnaire; TOMCP = Toronto Outcome Measure for Craniofacial Prosthetics, the 29-item version for new prosthesis users or 52-item version for previous users; OCQ = Outgoing Clinical Questionnaire; PEQ = Patient Evaluation Questionnaire; LASA = Linear Analogue Self Assessment; SF-8 = Short Form 8: Medical Outcomes Study Short-Form Health Survey; ICQ = Incoming Clinical Questionnaire. All questionnaires are available online.

Patients were excluded from study enrollment if they met any of the following exclusion criteria:

- Framework or implant/magnet retention
- Multiple tumor recurrences
- Hypersensitivity to adhesives or test materials
- Current systemic or topical facial steroid treatment
- Legally blind
- Expected to have further surgeries, radiation therapy, or other cytoreductive therapy (chemotherapy) over the next 10 months
- Have an active skin condition or disease
- High risk for infection

Sample Size

Sample size was estimated from results of an earlier phase II trial[22] and the Toronto Outcome Measure for Craniofacial Prosthetics.[25] Sample size calculations were made for noninferiority[26–28] using nQuery Advisor (version 4, Statistical Solutions). Assuming a 0.5 correlation between outcomes for the two prosthesis types, a sample size of 65 to 71 patients was needed to achieve 90% power to detect noninferiority with a $\Delta = 0.4$ on the six-level nonparametric measure of overall satisfaction. Six-month reports were prepared for Data Safety Monitoring Board review. The board recommended termination of the trial before the enrollment target was reached, owing to the futility of accrual since they determined that the patient population was so specific that the trial could not be completed in the allotted time. Consequently, only 42 patients were enrolled.

Study Intervention

In this crossover study, patients requiring an EMFP were randomly assigned to wear a silicone or CPE prosthesis for 4 months in the first arm of the study. They then wore a prosthesis made of the alternative material for 4 months in the second portion. Patients and clinicians rated each prosthesis using various evaluation instruments and questionnaires (see online appendices, Fig 2).

Randomization and Blinding

The Data Coordinating Center (Office of Clinical Research Services and Support, University of Louisville) generated a randomization set, stratified by site and previous experience with EMFPs, to determine which prosthesis material each patient wore first.

All personnel were trained in prosthesis fabrication and calibration of the evaluation procedures. During fabrication, the materials, especially acetic acid (silicone) and methyl methacrylate (CPE), have specific odors during fabrication, handling properties, and textures that can be discriminated by clinicians and patients, especially previous users. Patients were exposed to all materials used in the fabrication of both types of EMFPs regardless of which prosthesis was delivered. To maintain blinding, clinical evaluators wore gloves while performing the physical evaluation and only touched the prosthesis with cotton-tipped applicators when evaluating retention.

Prosthesis Fabrication

The silicone prosthesis was fabricated in 80% Silastic Adhesive A/20% MDX4-4210[29,30] with Georgia kaolin and oil-based pigments added,[31] laminated with a polyurethane sheet bonded with A-306 primer (Factor II, Dow Corning 1205),[32] and cured for 24 hours at room temperature. Extrinsic coloring with oil-based pigments in silicone adhesive type A was applied before delivery. The CPE was chosen by matching the patient's skin color to blankets of CPE made in 20 to 30 basic skin shades on the University of Louisville's rubber mill or custom coloring. The duplicated cast and mold were used to fabricate the CPE prosthesis in a regular or giant bronze flask (Hanau). A thin sheet of CPE containing rayon flocking, to simulate a ruddy or capillary-injected complexion, could be layered on the external surface. Pieces of CPE rubber were then cut to fill the mold cavity and heated in a pressure cooker at 115ºC (60 kPa or 10 psi) for 10 minutes. The process was repeated until the prosthesis was free of voids and minimal flash appeared at the parting lines. The surface was extrinsically colored with an oil-based pigment in a special flexible varnish. Ventilation was provided at both sites to evacuate volatile acetic acid (silicone) and methyl methacrylate (CPE) from the area around the patient's face during extrinsic coloring. Details of the CPE material and fabrication procedures will be reported in a separate publication.

After fabrication of both prostheses, the maxillofacial prosthodontist or anaplastologist at each site completed the Anaplastologist/Dental Laboratory Technician Questionnaire to compare the various features of the two materials (for complete questionnaires and results please see online appendices). Photographs were taken for the documentation of the prostheses and were used for the evaluation of the calibration among the clinical evaluators for the test/retest procedures.

Outcomes

The primary outcome was the proportion of patients that preferred the silicone to the CPE prosthesis. However, the trial was terminated early; consequently, the projected sample size was not reached and the utility of this outcome is limited. It was decided to assess for noninferiority of the CPE with the two secondary outcomes: the patients' overall satisfaction with the prostheses at the end of each study arm and the Toronto Outcome Measure for Craniofacial Prosthetics, a 52-item quality-of-life survey instrument-specific to this patient population. For both secondary outcomes, the difference between scores after wearing the silicone prosthesis for 4 months minus scores after wearing the CPE prosthesis for 4 months was analyzed since this was a crossover trial. Another consequence of closing the trial early was that the longevity of the EMFPs could not be evaluated fully.

Statistical Methods

Baseline characteristics were compared with unpaired *t* tests or chi-square tests as necessary. If distributional assumptions were not met, then alternative tests (Mann-Whitney rank sum test, Fisher exact test, etc) were used. The analysis of each material was a within-subject analysis (paired *t* tests or Wilcoxon signed rank tests). To further understand why one material was preferred over another, a general linear model was used to detect differences in the overall satisfaction between the two materials, exploring age, sex, center, previous experience wearing a prosthesis, location of the prosthesis (full or partial ear, orbital, or nose), and reason for treatment (cancer, trauma, or birth defect) as possible factors.

Results

Between October 2004 and December 2006, 124 patients were screened and 42 consented and were enrolled. Twenty patients were assigned randomly to wear the silicone prosthesis in the first arm and CPE in the second (silicone → CPE group); 22 received the CPE prosthesis in the first arm and silicone in the second (CPE → silicone group). Twenty-eight patients completed both arms of the study (Fig 3). Follow-up concluded in May 2007.

Patient characteristics are listed in Table 1. The most common causes for EMFPs were cancer (74%), trauma

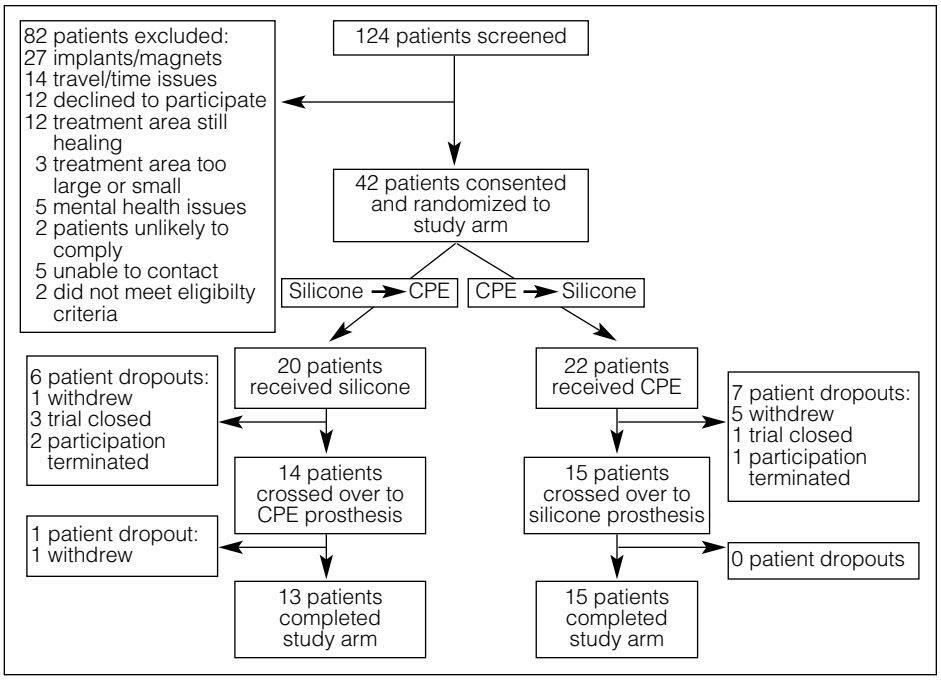

Fig 3 CONSORT flow chart showing enrollment of the study patients.

Table 1 Baseline Characteristics of Patients by Randomization Group

	Silicone → CPE (n = 20)	CPE → silicone (n = 22)	*P*
Age (y)	58 ± 16	59 ± 13	.886
Sex (male/female)	14/6	17/5	.592
Height (cm)	172 ± 13	178 ± 10	.327
Weight (kg)	79 ± 18	82 ± 14	.206
Center (Houston/Toronto)	14/6	15/7	
Race/ethnicity (%)			.197
Asian	2 (10)	0 (0)	
Black	1 (5)	0 (0)	
Hispanic	2 (10)	1 (5)	
White	15 (75)	21 (95)	
Reason for treatment (%)			.455
Cancer	14 (70)	17 (81)	
Trauma	4 (20)	1 (5)	
Birth defect	2 (10)	3 (14)	
Facial prosthesis type (%)			.121
Partial nasal	5 (25)	1 (5)	
Full nasal	2 (10)	7 (32)	
Partial ear	1 (5)	4 (18)	
Full ear	7 (35)	7 (32)	
Partial orbital	0 (0)	0 (0)	
Full orbital	5 (25)	3 (14)	
Smoking status (Y/N)	2/18	4/18	.449
Other tobacco use (Y/N)	2/17	2/20	.877
Drink alcohol (Y/N)	10/10	14/8	.373
Previous prosthesis user (Y/N)	12/8	13/9	.952
Facial skin lesions present (Y/N)	1/19	1/21	> .999
Infection present (Y/N)	0/20	0/22	–
Chemotherapy (Y/N)	2/18	4/18	.665
Radiation to the head/neck area (Y/N)	10/9	12/10	.976
Steroids in the last 6 months (Y/N)	0/20	0/22	–
Missing any teeth (Y/N)	15/5	18/4	.714
Bleed excessively when cut or after a tooth extraction (Y/N)	1/19	1/21	> .999
Cold sore or fever blisters (Y/N)	3/17	2/20	.656
Wear visual aids (Y/N)	19/1	16/6	.096
Wear hearing aids (Y/N)	2/18	2/20	> .999
Karnofsky performance scale (10–100)	99 ± 4	97 ± 9	.438
Mean TOMCP-29 score	2.5 ± 1.0	2.8 ± 1.8	.434
Total TOMCP-29 score (median [range])	67 (29–123)	61 (29–203)	.888

Y = yes; N = no; TOMCP-29 = 29-item version of the Toronto Outcome Measure for Craniofacial Prosthetics for new prosthetic users.

Table 2 Patient Evaluation Questionnaire Results*

	Silicone† (n= 28)	CPE† (n = 28)	P‡
How satisfied are you with this prosthesis? (0 = completely dissatisfied, 10 = completely satisfied)	9 (8–10)	7 (4–9)	.002
How many hours do you wear this prosthesis each day?	14 (12–24)	12.5 (9.5–24)	.294
On average, how many nights per week do you sleep wearing this prosthesis?	0.5 (0–5.5)	0 (0–6)	.395
How many layers of adhesive do you use with your prosthesis?	1 (1–2)	1 (1–2)	> .999
How comfortable is this prosthesis? (0 = completely comfortable, 10 = completely uncomfortable)	10 (8–10)	8 (4–10)	.002
Is there an odor from this prosthesis while you are wearing it? (0 = no odor, 10 = strong odor)	0 (0–0.5)	0 (0–0.5)	.897
Is there a sensation of heaviness when this prosthesis is worn? (0 = extremely light, 10 = extremely heavy)	0 (0–1)	1 (0–4)	.052
How satisfied are you with the overall appearance of this prosthesis? (0 = dissatisfied, 10 = satisfied)	9 (9–10)	7 (3.5–9)	< .001
Does this prosthesis now match your skin in color? (0 = does not match, 10 = completely matches)	9 (8–10)	4.5 (0.5–9)	< .001
Does this prosthesis now match your skin in texture? (0 = does not match, 10 = completely matches)	9 (8–10)	4.5 (0–8.5)	< .001

*The number of patients in the study groups included the 28 patients that completed both arms since this was a crossover study using within-person analyses. Questionnaire available online.
†Data reported as medians (25th percentile–75th percentile).
‡Wilcoxon signed-rank test.

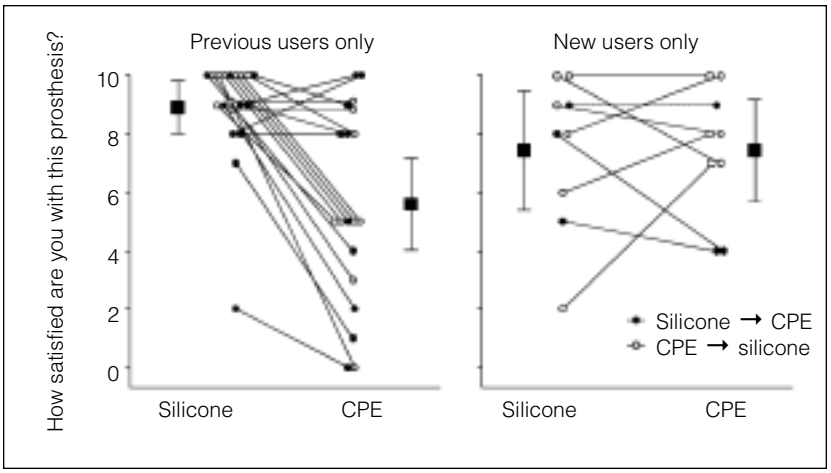

Fig 4 Patient satisfaction for both previous users and new users. Patient satisfaction was scored on a scale from 0 to 10. Twenty-eight users completed both arms of the study; 19 were previous users and 9 were new users. Scores from the same individual are linked by a solid line. All patients evaluated their first material at visit 4 and their second material at visit 6.

(12%), and birth defect (12%). Sixty-eight percent of participants had previous experience with silicone EMFPs.

Of the 28 participants who completed both study arms, 21 (75%) preferred the silicone EMFP, 5 (18%) preferred the CPE, and 2 (7%) expressed no preference (Table 2). Patients reported that the silicone EMFP was more comfortable, had a better overall appearance, and better matched their skin color and texture. When patients reported their overall satisfaction on a scale from 0 to 10 (0 = not satisfied, 10 = completely satisfied), they rated the silicone EMFP higher than the CPE (8.4 ± 2.2 vs 6.2 ± 3.1, difference: 2.2, 95% confidence interval [CI]: 0.9 to 3.6, $P = .017$). Previous users had a stronger preference for silicone (difference: 3.3, 95% CI: 1.7 to 4.9, $P = .001$), while the 9 patients new to EMFPs rated the two materials the same (difference: 0.0, 95% CI: –2.1 to 2.1, $P = 1.00$) (Fig 4).

Differences between the two study sites were evaluated. Generally, Houston patients were more satisfied with their prostheses than Toronto patients (7.9 ± 2.6 vs 5.2 ± 3.2, $P = .003$). The site difference was even larger when looking only at the silicone prostheses (9.2 ± 0.9 vs 5.7 ± 3.4, $P = .027$). Although Houston's patient satisfaction score for CPE was higher than Toronto's, the difference was not statistically significant (6.6 ± 3.0 vs 4.7 ± 3.2, $P = .183$).

Overall, patients rated their quality of life better when they wore the silicone EMFP than when they wore the CPE prosthesis (112 ± 63 vs 135 ± 65, difference: –23, 95% CI: –42 to 5, $P = .014$). When data from previous prosthesis users and new users were analyzed separately, previous users rated quality of life better after wearing the silicone prosthesis (difference: –30, 95% CI: –54 to 6, $P = .017$), whereas the nine patients new to EMFPs gave similar quality of life scores after each study arm (difference: –9, 95% CI: –41 to 23, $P = .525$). Detailed quality of life results will be reported in a separate publication.

Of the factors potentially responsible for users having a preference for silicone, only previous experience wearing an EMFP was associated with the difference in overall satisfaction significantly (mean effect of 3.3 units, $P = .014$).

Clinicians evaluating the two types of EMFPs at the beginning and end of each study arm indicated that, generally, prostheses made of CPE had thicker borders and greater color and texture differences from the adjacent skin than those made with silicone. In addition, there was more variation in the degree of glossiness and translucency in the prostheses made with CPE. The personnel who fabricated the prostheses rated the CPE prostheses as more complex and harder to manipulate, with a higher incidence of flaws and breaking during processing. Nevertheless, the overall average fabrication time was less for CPE (for complete questionnaires and results please see the online appendices).

Discussion

To the authors' knowledge, this is the first phase III trial comparing materials used for fabricating EMFPs. The crossover design was chosen because participants acted as their own controls. The results indicated that *(1)* patients' overall satisfaction was greater for silicone prostheses, *(2)* clinical evaluators scored the appearance of the EMFPs made of silicone higher than CPE, and *(3)* the dental professionals fabricating the EMFPs rated CPE more complex and harder to manipulate, with a higher incidence of flaws during processing.

Although silicone was preferred overall, an important finding was that patients new to wearing an EMFP, and hence not familiar with silicone, rated the two materials as equivalent, suggesting a potential bias by experienced users already familiar with silicone EMFPs (Fig 4). However, with only 9 new users completing both arms of the trial, conclusions about this population are not definitive. Nonetheless, these results are consistent with those of a previous phase II clinical trial using a multiple crossover design in which patients reported similar satisfaction with EMFPs fabricated with CPE and silicone.[22] Given the difficulties of recruitment for EMFP trials and the clinical need for experienced users with replacement prostheses, future studies will likely include both experienced and new users. Therefore, stratification of subjects by this variable is advised. While a trial of new users would eliminate the bias of previous material use, these individuals may need to withdraw from the study for additional cancer therapy or revision surgery. Also, the pool of eligible new users is relatively small.

Not every patient completed both arms of the study, which introduced a possible source of bias. In fact, patients in Toronto withdrew at a higher rate than those in Houston, possibly because the silicone formulation and methodology previously used in Toronto were not those chosen as the control formulation for this study. Accordingly, neither material—control nor experimental—was familiar to previous Toronto patients.

Clinicians at both sites had considerable experience working with silicone, but fabricating EMFPs from CPE was completely new. This experience gap may have influenced the quality of the CPE prostheses because mastering a new fabrication technique takes time and the time required depends on the experience of each fabricator. The Toronto fabricators expressed less satisfaction working with CPE than those in Houston, possibly because the fabricators in Toronto had to learn two new techniques (80% Silastic Adhesive A/20% MDX4-4210 with a polyurethane liner and CPE) versus only one (CPE) in Houston. Future studies using less experienced clinicians may be warranted.

The results of this and previous studies suggest that CPE offers some advantages over silicone for fabricating EMFPs, including that it *(1)* has higher edge, tear, and tensile strength; *(2)* is easy to adjust with rotary instruments or melting; *(3)* has an indefinite working time; *(4)* is resistant to the growth of microorganisms; *(5)* is much less expensive; *(6)* allows intrinsic color layering; and *(7)* requires less overall fabrication time. However, there are several disadvantages of CPE versus silicone as well. For example, CPE *(1)* requires a more complex technique, *(2)* is harder to manipulate in the mold, *(3)* has a higher incidence of flaws and breaks during processing, *(4)* is more stiff and less comfortable to the wearer, *(5)* has a worse overall appearance and color matching, and *(6)* has less color stability than silicone.

Conclusion

Most patients in this crossover phase III trial preferred the EMFP fabricated from the silicone elastomer, especially those who had worn a prosthetic device previously. However, CPE appears to be a suitable substitute for silicone for the fabrication of EMFPs in situations where the cost of silicone is prohibitive.

Acknowledgments

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