

Journal of Biomedical Optics

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Abstract. Laser tissue soldering is a method of repairing incisions. It involves the application of a biological solder to the approximated edges of the incision and heating it with a laser beam. A pilot clinical study was carried out on 10 patients who underwent laparoscopic cholecystectomy. Of the four abdominal incisions in each patient, two were sutured and two were laser soldered. Cicatrization, esthetical appearance, degree of pain, and pruritus in the incisions were examined on postoperative days 1, 7, and 30. The soldered wounds were watertight and healed well, with no discharge from these wounds or infection. The total closure time was equal in both methods, but the net soldering time was much shorter than suturing. There was no difference between the two types of wound closure with respect to the pain and pruritus on a follow-up of one month. Esthetically, the soldered incisions were estimated as good as the sutured ones. The present study confirmed that temperature-controlled laser soldering of human skin incisions is clinically feasible, and the results obtained were at least equivalent to those of standard suturing. © 2015 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: 10.1117/1.JBO.20.12.128002]

Keywords: clinical trial; laser soldering; skin; temperature control.

Paper 150458RR received Jul. 5, 2015; accepted for publication Nov. 17, 2015; published online Dec. 18, 2015; corrected Dec. 29, 2015.

1 Introduction

Historically, many research groups have used laser-bonding techniques to overcome the disadvantages of current surgical methods. Photothermal tissue bonding involves the heating of the edges of an incision gently to partially denature the collagen structure,¹ while photochemical tissue bonding makes use of a photosensitizing dye and a visible laser beam, which initiates a chemical reaction that regenerates protein crosslinks.² Two photothermal laser-bonding techniques have been developed: (1) laser tissue welding (LTW), in which the edges of an incision are approximated and then laser energy is applied to heat these edges and (2) laser tissue soldering (LTS), wherein a biological solder is spread over the incision prior to the laser heating. LTW experiments were conducted first, using different lasers, operating at different wavelengths under different conditions. Later, in order to reduce the thermal damage and increase the LTW strength, biological protein-based solders were introduced. LTS has been carried out with different types of lasers, together with various types of biological solders, such as fibrinogen,³ albumin,⁴ collagen,⁵ or chitosan.⁶ The solder was usually applied on the surface to be joined, and then laser energy was used to adhere the underlying wound edges together, and at the same time attaching the solder to the tissue surface, resulting in increased strength and generating a watertight seal. CO₂ laser beam at a wavelength in the middle infrared (IR) spectrum ($\lambda = 10.6 \mu\text{m}$) is highly absorbed by all biological solders and, therefore, can easily heat the solder and the underlying tissue. On the other hand, the radiation of other lasers used

(e.g., diode lasers emitting at the near-IR around 800 nm) is not absorbed by many of the solders. Therefore, special dyes (i.e., chromophores), designed to absorb the specific wavelengths of those lasers, were added to the solders so that they would absorb the laser radiation and generate heat.^{3,7,8}

LTW and LTS have been investigated in many different medical disciplines, including ophthalmology,⁹ urology,^{10,11} microsurgery,¹² neurosurgery,¹³ dermatology,¹⁴ and others.¹⁵ LTS is potentially a method that is easier to use than the existing closure methods, and it is expected that the healing process would be faster and, if performed correctly, will leave minimal scarring.¹⁶ Previous studies have usually examined the laser power, beam diameter, beam profile, power density, and the length of the procedure.^{17,18} Unfortunately, the absorption was dependent on the tissue type, its thickness, and state of hydration (which also changes from person to person), and therefore, it was very difficult to accurately control the conditions needed to obtain good results.¹⁵ This is the reason why most of the results reported in the literature could not be easily reproduced. Many of the researchers did not consider one of the most important parameters—the temperature of the heated spot. Tissue damage is exponentially dependent on the tissue temperature¹⁹ and linearly dependent on the heating time. Thus, a slight change in the heating time makes little difference. On the other hand, slight overheating may lead to severe thermal damage to the tissue, whereas heating to a low temperature may lead to weak bonding.²⁰ Therefore, the exact measurement of the temperature is crucial to the success of laser bonding of tissues. Measuring the tissue temperature under laboratory conditions²¹

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will never reflect the momentary true tissue temperature under operating room conditions. We therefore hypothesized that temperature monitoring and control are crucial for overcoming these problems.

The Applied Physics Group at Tel Aviv University has developed a temperature-controlled laser-bonding system based on a CO₂ laser operating at $\lambda = 10.6 \mu\text{m}$ and incorporating special optical fibers made of polycrystalline silver halides (AgClBr). These fibers are highly transparent over a very broad spectral range in the middle IR, with low losses (0.2 dB/m) at $\lambda = 10.6 \mu\text{m}$, and they are very flexible, insoluble in water, and biocompatible.²² The first generation LTS system with temperature control was developed in 1993,²³ and it made use of two silver halide fibers. One fiber, the delivery fiber, transmitted the radiation from the CO₂ laser to heat a spot on an incision. The second silver halide fiber, the sensing fiber, transmitted the IR radiation emitted from the heated tissue (i.e., black-body emission) to an IR detector. A computer program connected between the two devices in a negative feedback loop and maintained a desirable surface temperature T_s with an accuracy of $\pm 3^\circ\text{C}$. Recently, the system software was modified to give a better control of the tissue temperature. When tested on tissues *ex vivo*, the improved system showed faster and better temperature control.

For the LTS process, the edges of the incision were approximated, albumin solder was spread over the incision, and then the fiber-optic laser system was used to heat the incision area, spot-by-spot. It was found that the optimal conditions for laser soldering for all soft tissues were as follows: temperature $T_s = 60$ to 65°C and heating time $t = 10$ to 12 s .²⁴ This was an average temperature value, and the center was generally somewhat hotter than the periphery. However, the albumin layer absorbed most of the heat so that the maximal temperature at the tissue surface, under the albumin, was kept at the set temperature (Fig. 1), which prevented the thermal damage.

LTS has been carried out in our group using this system, on many different organs, in different animal models, using bovine albumin as a biological solder. This method was used to bond incisions in the cornea,²⁵ urinary bladder,²⁶ dura,²⁷ arteries,²⁸ and esophagus.²⁹ In most cases, the procedure was very fast and easy to carry out, compared with suturing. One of the great advantages of the fiber-optic system is that it can be used for endoscopic tissue bonding. Preliminary experiments have also been carried out in urology, for endoscopic bonding of incisions at the ureteropelvic junction.³⁰

Before embarking on a human study, a series of experiments, using the improved temperature-controlled laser-soldering

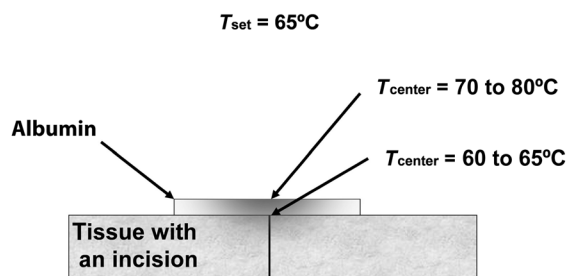


Fig. 1 For a set temperature of $T_s = 65^\circ\text{C}$, the maximal temperature at the topmost layer can reach tens of degrees above the set value, while at the albumin tissue interface, the temperature is much lower. Therefore, the albumin layer protects the tissue from overheating.

system, was carried out for bonding of incisions in the skins of large farm pigs,³¹ thus validating the performance of the system. Tensile strength measurements revealed that soldering was equivalent to or stronger than the other bonding methods. The laser-soldered incisions were examined histologically and exhibited no thermal damage. The healing time in the laser-soldered incisions was faster, and showed minimal scarring.

The excellent results achieved motivated us to proceed to a pilot clinical trial for soldering incisions in human skin. The study was performed on patients undergoing laparoscopic cholecystectomies for the following reasons: (1) In this operation, four incisions are made, which allows soldering of two and suturing of the other two incisions, each patient serving as its own control. (2) The Israeli Helsinki Committee required a preliminary study on small incisions, in a restricted number of patients.

2 Materials and Methods

2.1 Clinical Study

This pilot study was undertaken in the Department of Surgery B, Ha'Emek Medical Center, Afula, Israel. It was approved by the hospital and by the Israeli National (Ministry of Health) Helsinki Ethics Committees, approval # HTA 1884 (NLM Identifier NCT02149979). The study was designed as an open label prospective double-arm, pilot trial on volunteer patients. All patients received a fully explained study protocol and signed an informed consent document. Each patient served as his own control.

The study was carried out on 10 consecutive healthy patients, undergoing elective laparoscopic removal of an uncomplicated symptomatic gallbladder (cholecystolithiasis), under general anesthesia. All the surgical operations were performed by or under the supervision of the principal surgeon (D.K.). In each patient, four abdominal skin incisions were made for the introduction of trocars (J&J, Cincinnati, Ohio). These trocars are round air-tight tubes that serve as ports for inserting endoscopic instrumentation into the abdominal cavity. In this study, we used two 5-mm-diameter and two 10- to 12-mm-diameter trocars. The sites of introduction are shown in Fig. 2: #1

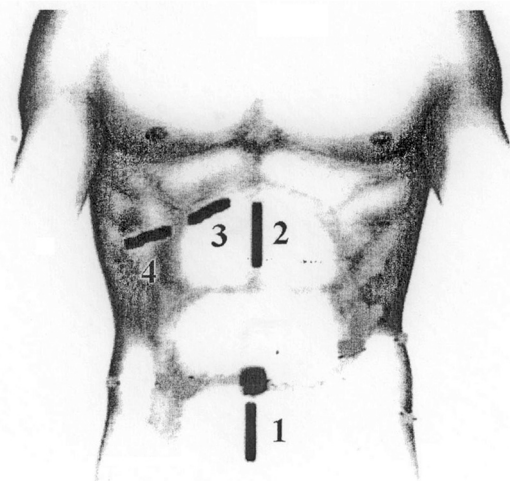


Fig. 2 The location of the skin incisions on the abdomen: incisions 1 and 2 were 10 mm long, and incisions 3 and 4 were 20 mm long. The patients were divided into two groups: in group I, cuts 2 and 3 were sutured, and cuts 1 and 4 were soldered; and in group II, cuts 1 and 4 were sutured, and cuts 2 and 3 were soldered.

below the umbilicus, #2 at the upper midline, #3 just below the median part of the right costo-chondral arc, and #4 just below the anterior lateral part of the right costo-chondral arc. Initially, incisions 1 and 2 were 20 mm long and incisions 3 and 4 were 10 mm long. To extirpate the gallbladder, one of the incisions had to be lengthened. Thus, the final lengths of the incisions varied between 10 and 43 mm. At the end of the procedure, the fatty subcutaneous layers were approximated by a single subcutaneous Vicryl suture (Ethicon Inc., Somerville, New Jersey). The patients were divided into two groups: in group I (patients # 1, 3, 5, 7, and 9), incisions 1 and 4 were soldered, and incisions 2 and 3 were sutured. The inverse method of closure was done in group II (patients # 2, 4, 6, 8, and 10). For skin suturing, interrupted Nylon 4/0 sutures (Ethicon Inc.) were used and placed at an approximate distance of 5 mm in between two neighboring sutures. The laser-soldered incisions were approximated by a mechanical vacuum device (see the figure in our previous publication³¹ and patent³²). This device consisted of two arms that had been placed longitudinally on both sides of the incision and were attached to the tissue surface using vacuum. The arms pulled the incision edges toward each other, to provide an optimal approximation. A thin layer (0.25 ± 0.05 mm) of human albumin was applied over the approximated edges and then the improved fiber-optic temperature-controlled laser-soldering system was operated. During the procedure, the laser power changed between 0 and 0.7 W (depending on the particular conditions). The working distance between the distal tips of the fibers and each incision was 5 ± 0.5 mm, giving rise to a spot diameter of ~ 3 mm. The temperature control was set to $T_s = 65^\circ\text{C}$. On each spot, the set temperature was immediately stabilized and then maintained for ~ 10 s, before the distal tip was moved to the next neighboring spot, with a slight overlap of 0.5 to 1 mm. The visual signs of a slight bleach of the albumin indicated the need to move to the next spot. The time required for each procedure was recorded. For the soldered incisions, two time lags were recorded: the total time required (which involves the approximation of the incision edges and the laser-soldering process) and the net time required for performing the soldering itself. On average, it took a total of ~ 1 to 2 min (net time) to bond each incision. At the end of the procedure, the approximation device was removed and adhesive tapes (Steri-Strip, 3M, Maplewood, Minnesota) were placed on both the sutured and the laser-bonded incisions. These tapes were placed in order to prevent unintentional friction between the incisions and the patient's cloths. All the suturing and the laser-soldering procedures were performed by the same surgeon (D.S.).

On postoperative day (POD) 2, the tapes covering the wounds were removed and the patients were asked to gently wash the incision. The sutures were removed on POD 7. On PODs 1, 7, and 30, the patients indicated the strength of pain in each incision, using a visual analog scale 1 to 10. The amount of pruritus in each wound and the requirement of analgesics, using an analog scale of 1 to 5, were also recorded. Each wound was evaluated for bleeding, oozing, discharge, redness, edema, infection, subcutaneous collection, dehiscence, step-off borders (i.e., the edges are not on the same plane), contour irregularities (wrinkled edges), scar width, edge inversion, and excessive inflammation. The wounds were graded for overall cosmetic appearance. Follow-up of the surgical incision healing was documented by pictures of the abdomen taken on PODs 2, 7, and 30. In four patients, we were able to obtain pictures on

POD 90 as well. On all PODs, the patients were also asked to estimate the esthetical appearance of the wounds, by comparing the ones that were sutured to the ones that were soldered.

2.2 Laser Soldering System

Soldering was performed with our improved fiber-optic temperature-controlled laser system. It consisted of two silver halide core-only fibers (NA = 0.23), each of diameter 0.7 mm. The CO₂ laser (Model 40C, Sharplan Lasers Inc., Warwick, Rhode Island) beam at wavelength $\lambda = 10.6 \mu\text{m}$ was focused using a ZnSe lens, to the proximal tip of one fiber. The beam exiting from the distal tip served to heat a spot on the incision. The heated spot emitted IR radiation whose intensity was proportional to the temperature of the spot and this radiation entered the distal end of the second fiber. The radiation reached the proximal tip of the second fiber and was then coupled to an IR radiometer, based on a pyroelectric detector (Model P3782-05, Hamamatsu Photonics, Hamamatsu, Japan). The reading of the radiometer served for determining the temperature of the heated spot.

2.3 Human Serum Albumin

For the clinical experiments, we used an aqueous solution of human albumin. We placed 1 ml of 25% human serum albumin (Omrix Biopharmaceuticals Ltd., Tel Aviv, Israel) in each of a lyophilization vial. The vials were vacuum dried for 6.5 h under a pressure of 50 mbar at a shelf temperature of 14°C . The final concentration of albumin was 40 to 45% w/v.

2.4 Statistical Study

The results for the two groups (laser soldered and sutured) were compared, using the two-sided Student's *t* test for unpaired or paired data—as appropriate. A *p* value < 0.05 was considered statistically significant.

3 Results

Figure 3 shows the temperature control that was achieved in a spot on one of the incisions, during the clinical trial. The tissue temperature easily stabilized at the set temperature value of $T_s = 65^\circ\text{C}$ with a $\pm 5^\circ\text{C}$ error. Similar temperature stabilizations were observed in all the other laser-soldering procedures.

The patient characteristics are provided in Table 1. All 20 incisions, except one, were successfully laser soldered. The

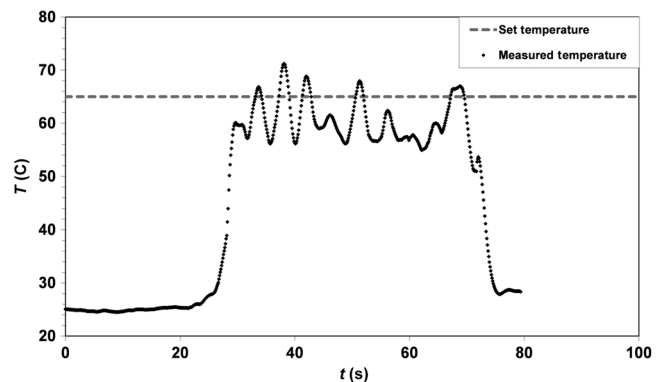


Fig. 3 A typical graph showing the temperature stabilization on the set value of $T_s = 65^\circ\text{C}$.

Table 1 The patient characteristics.

Patient #	Gender (M/F)	Age (years)	Weight (kg)	Height (cm)	Fitzpatrick (grade)	Skin (color)
1	F	24	58	163	III	Beige olive
2	F	52	74		III	Beige olive
3	F	17	78	158	III	Fair pale
4	M	56	65	164	II	Fair pale
5	F	52	88	168	II	Fair pale
6	F	52	85	163	III	Fair pale
7	F	37	72	163	II	Beige olive
8	M	32	130		II	Brown
9	F	21	95	172	II	Pale
10	F	31	59	162	III	Beige

single incision in which soldering initially failed was immediately resoldered successfully. The mean of the combined lengths of the sutured and the soldered incisions of all patients was comparable: 40.7 ± 6.8 versus 40.0 ± 7.2 mm (mean \pm s.d.), with $p = 0.84$. The mean of the combined time of closure was

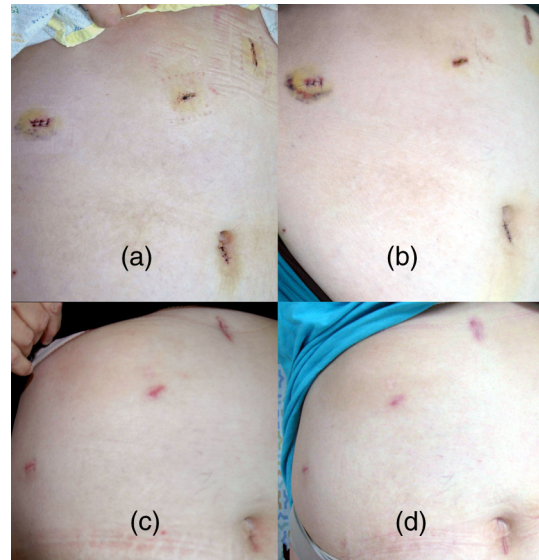


Fig. 4 The appearance of all four wounds in one of the patients on postoperative days (POD): (a) POD 2, (b) POD 7, (c) POD 30, and (d) POD 90.

calculated by s/mm. The combined suture time, the combined total soldering time, and the combined net soldering time for each patient are given in Table 2.

The suturing time and the total soldering time were comparable ($p = 0.062$), while the net soldering time was much shorter than the suturing time ($p = 0.001$). On POD 2, there were no stains on the tapes that covered the laser-soldered wounds, unlike the tapes that covered the sutured wounds. This proves the watertight nature of the laser-sealed wounds, which remained totally dry during the entire postoperative

Table 2 The combined suturing time, the combined total soldering time, and the combined net soldering time for each patient (t = time, l = length, AVG = average, and STD = standard deviation).

	Suturing			Soldering—net			Soldering—total		
	t (s)	l (mm)	t (s/mm)	t (s)	l (mm)	t (s/mm)	t (s)	l (mm)	t (s/mm)
1	256	41	6.2	214	41	5.2	389	41	9.5
2	330	45	7.3	230	40	5.8	405	40	10.1
3	284	32	8.9	161	57	2.8	364	57	6.4
4	310	48	6.5	216	45	4.8	515	45	11.4
5	266	40	6.7	188	40	4.7	343	40	8.6
6	276	41	6.7	225	38	5.9	479	38	12.6
7	285	54	5.3	127	37	3.4	525	37	14.2
8	304	38	8.0	108	33	3.3	340	33	10.3
9	278	34	8.2	168	38	4.4	309	38	8.1
10	300	34	8.8	115	31	3.7	184	31	5.9
AVG	288.9	40.7	7.3	175.2	40.0	4.4	385.3	40.0	9.7
STDEV	22.2	6.8	1.2	46.6	7.2	1.1	103.4	7.2	2.6

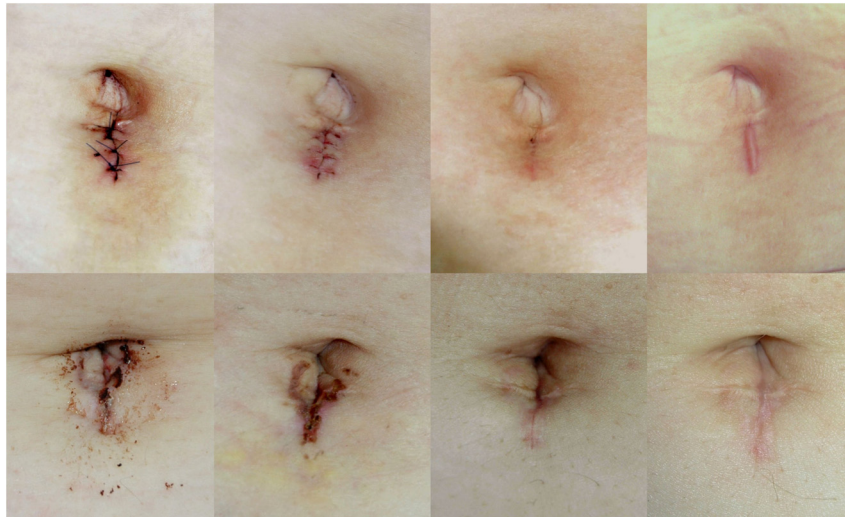


Fig. 5 A close-up appearance of two umbilical wounds, sutured in the upper row and soldered in the lower row, on PODs 2, 7, 30, and 90 (from left to right).

period. Figure 4 shows the appearance of the incisions, in one of the patients, on PODs 2, 7, 30, and 90. The most problematic incision for soldering was the umbilical, and a close view of this incision for the four PODs in two patients, soldered in one and sutured in the other, is given in Fig. 5.

The results of the pain evaluation for the sutured wounds in group I were compared to the equivalent results in group II, for each of the three PODs, using the Student's *t* test for unpaired data. The same comparison was made for the soldered wounds in the same groups. As there was no statistical difference between the two groups, the pain score for all the sutured wounds was compared to that of all soldered wounds, using the Student's *t* test for paired data. All these results are given in Table 3 and show that there was no statistical difference between the different groups and between the closure methods used. The same evaluations made for pruritus are given in Table 4, which (except for POD 7) showed no difference between the groups. The esthetical estimation of the wounds

by the patients for POD 7 and POD 30 are given in Table 5, showing a preference for the soldered incisions on POD 7.

4 Discussion

The classical method for closure of skin incisions is by using sutures, which are inexpensive, reliable, and readily available. However, there are some complications associated with this technique: foreign body reaction to sutures, development of transverse scarring, and the fact that the suture line may become a port of entry for microorganisms. The use of metal clips involves similar problems. We postulated that laser soldering may at least overcome some of the drawbacks of suturing.

The laser closure technique applies gentle heating to the approximated cut edges and speeds up the tissue healing process, as already shown.¹⁴ LTW and LTS methods were already described. Many groups have presented impressive results using different types of lasers for laser soldering of a large variety of tissues.¹⁵ However, the results were not always consistent,

Table 3 The pain score (1 = no pain, 10 = severe pain), comparing group I to group II, and the total sutured wounds to all soldered wounds.

		Group I versus group II		Sutures versus soldering		
POD 1	Sutures	Group I	7.80 ± 7.26	<i>p</i> = 0.8524	7.40 ± 6.22	<i>p</i> = 0.4809
		Group II	7.00 ± 5.83			
	Soldering	Group I	4.40 ± 6.80	<i>p</i> = 0.6562	5.40 ± 6.54	
		Group II	6.40 ± 6.88			
POD 7	Sutures	Group I	3.60 ± 5.68	<i>p</i> = 0.5071	4.50 ± 3.98	<i>p</i> = 0.1719
		Group II	5.40 ± 1.14			
	Soldering	Group I	1.60 ± 3.05	<i>p</i> = 0.5212	2.20 ± 2.74	
		Group II	2.80 ± 2.59			
POD 30	Sutures	Group I	2.20 ± 2.17	<i>p</i> = 0.5565	1.80 ± 1.99	<i>p</i> = 0.4862
		Group II	1.40 ± 1.95			
	Soldering	Group I	0.80 ± 1.30	<i>p</i> = 0.3972	1.20 ± 1.40	
		Group II	1.60 ± 1.52			

Table 4 The pruritus score (1 = no pruritus, 10 = severe pruritus), comparing group I to group II, and comparing the total sutured wounds to all soldered wounds.

		Group I versus group II			Sutures versus soldering	
POD 1	Sutures	Group I	2.60 ± 0.89	<i>p</i> = 0.2275	2.30 ± 0.67	<i>p</i> = 0.7364
		Group II	2.00 ± 0.00			
	Soldering	Group I	2.40 ± 0.89	<i>p</i> = 0.3466	2.20 ± 0.63	
		Group II	2.00 ± 0.00			
POD 7	Sutures	Group I	6.00 ± 2.45	<i>p</i> = 0.2049	5.00 ± 2.40	<i>p</i> = 0.0141
		Group II	4.00 ± 2.12			
	Soldering	Group I	3.20 ± 2.68	<i>p</i> = 1.0000	3.20 ± 2.30	
		Group II	3.20 ± 2.17			
POD 30	Sutures	Group I	2.40 ± 0.55	<i>p</i> = 0.7655	2.50 ± 0.97	<i>p</i> = 1.0000
		Group II	2.60 ± 1.34			
	Soldering	Group I	2.40 ± 0.89	<i>p</i> = 0.7328	2.50 ± 0.85	
		Group II	2.60 ± 0.89			

Table 5 The esthetical estimation of the wounds by the patients.

	Sutures	Soldering	No preference
POD 7	0	7	3
POD 30	4	3	3

and in our opinion, the failure was related to a lack of temperature monitoring and control of the incision throughout the process. In order to overcome this problem, we first developed a sensor based on a mid-IR fiber and an IR detector that was capable of monitoring the temperature of a heated spot.²³ The heating laser beam was coupled to a second mid-IR fiber and both fibers were inserted into one hand-piece to be held by the surgeon. The laser and the sensor were connected to a computer, where a control program controlled the laser power and maintained the average surface temperature at the desired value of 65°C. In the past, we carried out several successful animal experiments.^{33,34} In particular, we carried out temperature-controlled laser soldering of incisions on the backs of large farm pigs³¹ and demonstrated a high-quality reparative outcome. In the present work, we embarked on a pilot clinical study, where each patient served as its own control.

We found that the total time required for soldering was equivalent to that required for suturing. However, there was a clear statistical difference in the comparison made with the net soldering time—which was shorter than the suturing time. We believe that in the future, when a better method of approximation is developed (like using an instrument that will stretch the edges of the incision, thus achieving a rapid adjustment of its borders), the total time of soldering will be reduced.

Except for POD 7 for pruritus, no statistical difference was found between the groups for pain and pruritus, for each POD. Possibly, the reason was the small number of participants. If we consider the visual appearance of the wounds, as evaluated by the patients themselves, no practical difference was reported between the two types of closure.

Some of the laser-soldered incisions were located next to the patient’s umbilicus—a very challenging area, where the skin is

not a flat surface. The successful bonding of these incisions demonstrated the ability of the LTS system to operate in situations that are not ideal. This result is attributed to the improved automatic system, which reduced the sensitivity to working distance, compensating for small deviations that may have been made by the surgeon, and thus making possible the bonding of incisions of different curvatures.

In conclusion, the data obtained in this pilot study showed that the temperature-controlled laser-soldering method successfully bonded human skin incisions, in flat and curved surfaces. It confirmed that the results produced by soldering are at least equivalent to suturing.

Further large-scale clinical studies are necessary to establish better statistical results and to validate the use of temperature-controlled laser soldering of longer skin incisions. As the last phase of the wound healing (remodeling and contraction) can continue for six months or longer,³⁵ a much longer follow-up is required to compare the final appearance of soldered to that of sutured incisions.

Recently, we have further improved the laser-soldering system, by replacing the two fibers by a single fiber. With this system, we obtained excellent results for bonding of incisions in the cornea.³⁶ We expect that it will improve the bonding of skin incisions as well, shortening the procedure and perhaps resulting in even less scarring.

Acknowledgments

The authors would like to thank Mr. Arie Levite and the physicians and nurses at Ha’Emek Medical Center, who participated in the clinical trials, for their great help.

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