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Review article

Laser tissue soldering of the gastrointestinal tract: A systematic review LTS of the gastrointestinal tract

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ABSTRACT

Background: Laser Tissue Soldering (LTS) is a promising tissue bonding technique in which a solder is applied between the tissues and then irradiated by laser, causing it to solidify and form links with the tissue.
Methods: A comprehensive systematic review summarizing the state of research of LTS in the gastrointestinal tract.
Results: Most studies were conducted on large animal tissues, using liquid proteinaceous solder, and irradiated by a continuous wave laser at 808 nm. LTS can provide better sealing and burst pressure than conventional methods. The application of LTS on top of or in addition to sutures showed an impressive increase in burst pressures. LTS may decrease the inflammatory and foreign body reaction caused by sutures.
Conclusions: LTS has strong potential to be applied in a clinical setting in leak prevention and in closure of gastrointestinal structures as an adjunct or additional anastomotic technology, decreasing leak rates, morbidity, and mortality.

1. Introduction

Anastomotic leaks following gastrointestinal tumor resections, bariatric surgery, trauma surgery and others are a major source of concern for clinicians and patients alike. In a recent NSQIP database study 45.8% required additional operations, hospitalization period was lengthened to more than twice as long, and mortality rates were significantly increased [1]. In addition, leaks lead to a significant financial burden ($56,349 vs $16,085 with no leak in one study) [1]. The risk of anastomotic leak varies in different locations in the gastrointestinal tract, ranging from 1.6% (stomach) through 5.5% (small intestine), 6% (colon), 7% (rectum) and 13.5% (esophagus) [1]. In the face of this reality, there is a strong interest in the development of techniques for better tissue approximation and sealing, and improved leak rates [2,3].

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Common tissue bonding methods such as sutures or staples exert tension and compression forces on the bonded tissue. This may result in the formation of gaps in the anastomotic line, resulting in anastomotic leaks [2]. Other common risk factors for leaks include impaired anastomotic blood supply, previous chemo-radiation, intraoperative hypotension, smoking and others. Recently, it has been shown that certain bacterial strains in the GI tract produce substances (e.g., matrix metalloproteinases), that inhibit stromal regeneration [4].

Laser technology has been used as an alternative method for tissue bonding in different tissues, with recent-years studies on skin [5], cornea [6], oral mucosa [7], and even nerves [8]. Laser tissue bonding through thermal reaction can be performed by 2 main methods: Laser Tissue Welding (LTW) in which a laser diode is used to heat the tissue edges; and Laser Tissue Soldering (LTS) in which the bond is generated through the heating of a dedicated proteinaceous solder material. Laser tissue bonding can also be formed in a non-thermal method, by using photoactive dye (Photochemical Tissue Bonding - PTB) will not be addressed in this article [9,10].

A solder can be described as a solution encompassing a proteinaceous component in a hydrophilic solvent. The purpose of the proteinaceous component is to undergo denaturation when heated by a laser, and form bonds with the native tissue proteins. LTS has been attempted and clinically applied to other tube-like structures such as blood vessels [11] and ureters [12], resulting in lower complication rates. Different tissues have different physical properties affecting the bonding technique. This is affected by factors such as absorption coefficients for example melanin in the skin absorbs differently than bowel wall. Required tissue depth penetration also changes between different tissues. In skin for example, only superficial penetration is required whereas in bowel deeper penetration is needed to achieve the larger bonding surface. Blood vessels have different properties than bowel, with a thinner wall and smaller caliber and require a laser with little penetration and large absorption. The gastrointestinal tract tissue is made of several markedly different layers. This diversity, together with other tissue characteristics (bacterial environment, motility and more), differentiate the GI tissue from other tissues and make it a more complex tissue to bond. In general, a laser with a wavelength allowing for deeper penetration with less surface absorption should be utilized.

LTS of the gastrointestinal system has the potential to overcome some of the disadvantages of sutures or staples and achieve a strong waterproof anastomosis with a possible reduction in anastomotic leak rates. Laser tissue bonding may also present a promising alternative to suturing in areas of limited accessibility using laparoscopic [13,14] and robot-assisted surgery [15,16]. In these applications, distorted [17] or missing [18,19] haptic feedback can increase the chances of tearing the tissue or suture, leading to anastomotic leaks. This results in a requirement for significant technical skill in robot-assisted suturing [20–22]. To date, robotic-assisted laser tissue welding has been demonstrated in ophthalmic surgery for welding of the sclera [23] and the cornea [24]. However, comprehensive knowledge of how to best perform LTS in the GI tract is missing.

To address this gap in the literature in the face of ongoing research, and with the clinical potential becoming practical, we aimed to provide an up-to-date comprehensive review of LTS in the gastrointestinal tract. Specifically, we focus on soldering in different GI segments and the technical parameters of LTS that can maximize the chances of successful bonding.

2. Methods

We performed a comprehensive systematic review including all trials in which LTS was used to bind tissues in the gastrointestinal tract. The study was registered on the International prospective register of systematic reviews (PROSPERO) database (ID number: CRD42020167788) prior to execution. Our study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement, and the Systematic Review Center for Laboratory animal Experimentation (SYRCLE) guidelines [25–27] (checklists available in supplementary figures 1 and 2 respectively).

2.1. Search strategy

A literature search was performed on February 4, 2022, in each of the following databases: PubMed, Embase and the Cochrane Library. A combination of different MeSH/Emtree categories/free text terms regarding LTS and complemental terms regarding gastrointestinal tissues was undertaken to identify a wide range of articles regarding LTS of the gastrointestinal tract. The following MeSH/Emtree categories were searched: “laser therapy”, “laser coagulation”, or free text terms: “laser welding”, “tissue welding”, “laser soldering”, “tissue soldering”, “laser fusion”, “laser adhesive” and “laser sealing”. Each of these was searched in combination with each of the following complemental terms: “gastrointestinal”, “esophagus”, “stomach”, “gastric”, “bowel”, “intestine”, “colon” and “rectum”. The process detailed above was identically executed in all databases, apart from the replacement of the MeSH category of “laser therapy” with the Emtree category of “laser thermotherapy” in the Embase database. The number of initial search results for each combination is available in supplementary figure 3.

For all complemental terms (i.e., terms regarding gastrointestinal tissues) the search was broadened to also include words that start with the term. For example, in the PubMed database the text search for the combination of the MeSH category: “laser therapy” and the complemental term: “intestine” was carried out as: *“Laser Therapy"[Mesh] AND intestine**. In a similar manner, the search for the combination of the free text term: “laser soldering” and the complemental term: “colon” was carried out as: *“laser soldering” AND colon**. All search results were combined into one database and duplications removed using the Covidence software (Veritas Health Innovation, Melbourne, Australia) [28].

2.2. Screening process

All initially eligible studies were screened for relevance, in parallel, by two independent analysts (I.A. and N.A.), using the

Covidence software (Veritas Health Innovation, Melbourne, Australia) [28]. Disagreements were resolved by discussion and a third senior reviewer (U.N.). We included original articles concerning LTS experiments that were performed on tissues of the gastrointestinal tract (i.e., esophagus, stomach, small intestine, appendix, colon, and rectum) both ex-vivo and in-vivo. Only English written, peer-reviewed, full text articles were included. If the same experiment or data was included in more than one article, only the most relevant and elaborated one was included, to avoid bias. Due to possible misuse of terminology, articles regarding tissue welding were initially included into the search but were later removed during full-text screening. After screening completion, all references and citations of included records were also screened to increase the effectivity of the search and maximize the probability for detection of relevant material.

2.3. Bias assessment

A bias assessment was conducted by two independent analysts (N.A. and I.A.) for all included records using the Joanna Briggs Institute Critical Appraisal Tool Checklist for Quasi-Experimental Studies (non-randomized experimental studies) [29]. The checklist is composed of nine questions, which can be answered by one of the following: "yes", "no", "unclear", and "not applicable". The answer "yes" was considered positive (i.e., reduces the risk of bias), whereas "no" or "unclear" regarded as negative. The answer "not applicable" was not calculated in the total score as it was irrelevant for the assessment of the particular record. All studies that met the initial criteria were graded by the percentile of positive answers out of all the relevant answers. Articles graded 80% and above were included in the final analysis. The risk of bias assessment tool checklist is available in supplementary figure 4.

2.4. Data extraction

All included records were fully scanned by two independent analysts, to minimize the risk of errors. The following information was collected: year of publication, animal model, tissue used, set up (i.e., in-vivo or ex-vivo), procedure (type of bonding: i.e., anastomotic closure). The following details were collected regarding the aspects of LTS: laser system (type, power, power density, wavelength, heat generated), mode (continuous or pulsed), solder (composition and state of matter). Outcome evaluation was assessed for tensile strength measured for bond separation, burst pressure, micro-assessment (histological stains and microscopic instruments), macro-assessment (clinical assessment for complications), days from procedure (for in-vivo studies), and control (what type of control was used).

The procedure types were classified into one of the following: "tissue bonding", "incision", or "anastomosis". "Tissue bonding" refers to the bonding of rectangular tissue slices, "Incision" to the sealing of an incision in the wall of a whole hollow organ, and "anastomosis" to the complete rejoining of a gastrointestinal tubular structure. The procedures were additionally classified as "closure" or "reinforcement", referring to bonding by LTS alone and application of LTS on top of sutures respectfully.

Adequate mechanical strength is a crucial component of a successful procedure. Accepted measures for mechanical strength of anastomoses are both tensile strength and burst pressure, which also portray the integrity and fluid-tight closure of the anastomosis [30,31]. A variety of units have been utilized for providing data for tensile strength and burst pressure by different studies. To provide a

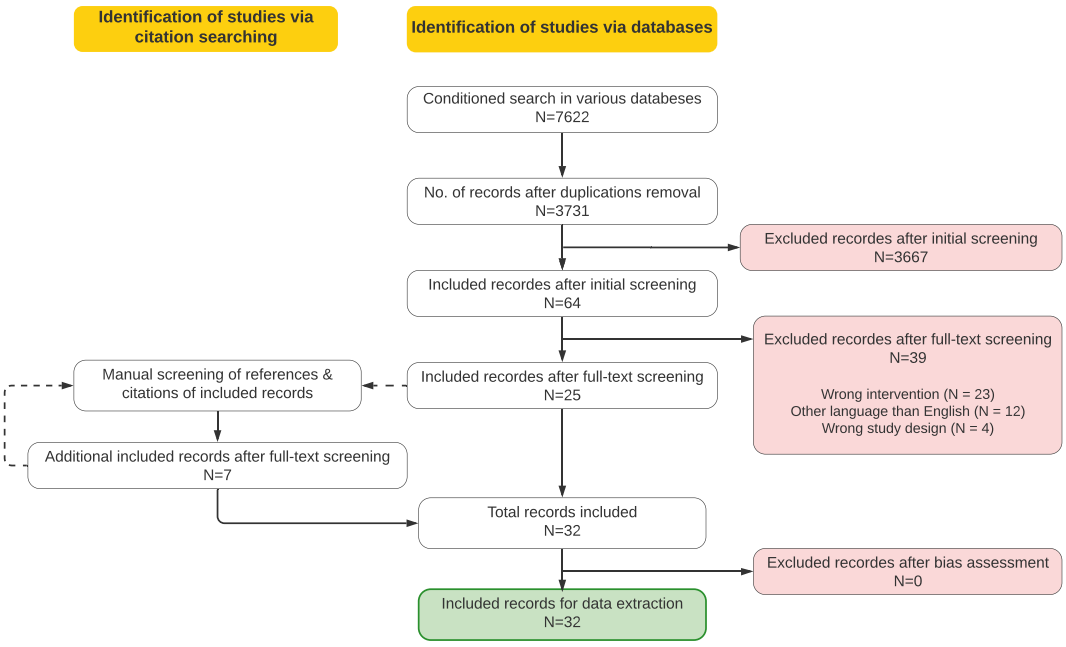

Fig. 1. Flowchart describing the studies selection process.

Table 1A
LTS of the small intestine.

Article	General Information		Laser					Solder	Outcomes						
	Model (Set Up)	Procedure	Type	Power W (Mode)	Power Density W/cm^2	Wave-length nm	Heat C°	Composition (State of Matter)	Days from procedure	Control	Tensile Strength, (n) KPa		Burst Pressure, (n) mmHg		Micro
											Control	Intervention	Control	Intervention	
Perito et al., 1993 [48]	rat (IN)	bonding to bladder	CO2	0.5 (PW)	1000	1060	–	HSA 25% (L)	14	sutures	–	–	(5) 134	(10) 136	H&E
Lauto et al., 1998 [49]	rat (EX)	tissue bonding	diode	0.27 (CW)	–	810	–	BSA 75% + ICG 0.25% (S)	0	–	–	(4) 18.61#	–	–	–
Lauto et al., 1999 [33]	dog (EX)	tissue bonding	GaAs diode	_ (CW)	–	810	–	2 layers: white-BSA 72%, black-BSA 72% + CB 0.39% (SF)	0	1 layer (black)	(10) 29.52#	(10) 27.44#	–	–	H&E + Masson
Bleustein, Walker et al., 2000 [50]	dog (EX)	tissue bonding	Nd:YAG	2 (CW)	–	1320	–	BSA 48% + HPMC 3% (S/L)	0	–	–	(?) 52#	–	–	Masson
Bleustein, Felsen et al., 2000 [51]	dog (EX)	tissue bonding	Nd:YAG	2 (CW)	–	1320	–	BSA 50% (L)	0	–	–	(15) 43#	–	–	–
Landma et al., 2000 [52]	pig (EX)	tissue bonding	KTP	2 (PW)	–	532	–	AL 50% (L)	0	sutures	(?) 379*#	(?) 36*#	–	–	–
Lauto et al., 2001 [53]	dog (EX)	tissue bonding	GaAlAs diode	0.14 (CW)	–	810	50	BSA 65% + CB 0.22% (SF)	0	–	–	(30) 44.31#	–	–	Masson + TEM
Stewart et al., 2001 [54]	dog (EX)	tissue bonding	Nd:YAG	2 (CW)	–	1320	82	PCAPPS 23% (L)	0	–	–	(23) ~11.6	–	–	Masson
Lauto et al., 2003 [34]	dog (EX)	tissue bonding	GaAlAs diode	0.17 (CW)	–	808	62	2 layers: white-BSA 65%, black-BSA 65% + CB 0.25% (SF)	0	–	–	(14) 26.16#	–	–	–
Ware et al., 2003 [55]	Pig (EX)	tissue bonding	diode	–	21	808	–	AL 45% + ICG 0.5 mg/ml (L)	0	–	–	(14) 29.5	–	–	–
Lauto et al., 2004 [35]	sheep (EX)	tissue bonding	GaAlAs diode	0.17 (CW)	–	808	–	BSA 62% + ICG 0.25% + G 0.38% (SF)	0	LTS w/ o G	(30) 8.59*#	(30) 16.66*#	–	–	–
Simhon et al., 2004 [46]	rabbit (IN)	anastomosis closure	CO2	_ (CW)	2.1	1060	65	AL (SS) + BSA 50% (L)	14	sutures	–	–	–	–	H&E

(*continued on next page*)

Table 1A (*continued*)

Article	General Information		Laser					Solder	Outcomes						
	Model (Set Up)	Procedure	Type	Power W (Mode)	Power Density W/cm^2	Wave-length nm	Heat C°	Composition (State of Matter)	Days from procedure	Control	Tensile Strength, (n) KPa		Burst Pressure, (n) mmHg		Micro
											Control	Intervention	Control	Intervention	
Lauto et al., 2005 [56]	sheep (EX)	tissue bonding	GaAlAs diode	0.12 (CW)	15	808	57	CH 2% + AA 2% + ICG 0.02% (SF)	0	film w/ o laser	(30) 2.4	(30) 14.7	–	–	–
Lauto et al., 2007 [57]	sheep (EX)	tissue bonding	GaAlAs diode	0.12 (CW)	15	808	–	CH 1.8% + AA 2% + ICG 0.02% (SF)	0	film w/ o laser	(30) 1.9	(30) 14.7	–	–	SEM
Lauto et al., 2008 [58]	sheep (EX)	tissue bonding	diode	0.12 (CW)	15	808	–	CH 1.8% + AA 2% + ICG 0.02% (SF)	0	film w/ o laser	(10) 1.3	(10) 13	–	–	H&E + SEM
Lauto 2009 [44]	sheep (EX)	tissue bonding	diode	0.12 (CW)	15	808	59	CH 2% + AA 2% + ICG 0.02% + SIS (SF)	0	–	–	(15) 9.58	–	–	–
Spector et al., 2009 [37]	pig (EX)	anastomosis closure	GaAs	2.7 (CW)	30	828	75	AL 40% + ICG 0.3 mg/g (L) + AL 90% (SS)	0	sutures	–	–	(5) 83	(15) 170	–
Foster et al., 2010 [43]	sheep (EX)	tissue bonding	GaAlAs diode	0.12 (CW)	15	808	54	CH 2% + AA 2% + V 5% (L) + CH + ICG 0.02% (SF)	0	LTS w/ o V	(10) 17.8	(10) 16.5	–	–	H&E + SEM
Rabi et al., 2010 [59]	pig (EX)	tissue bonding	GaAs	1 (CW)	57	828	150	AL 45% + ICG 0.3 mg/g (L)	0	–	–	(7) 121	–	–	–
Huang et al., 2013 [60]	pig (EX)	tissue bonding + incision closure	TiSa	_ (CW)	20	800	61	ELP + GNR 5.4% (L)	0	intact	(11) 450#	(9) 220#	(3) 620.57#	(3) 299.94#	–
Urie et al., 2015 [38]	pig (EX)	tissue bonding + incision closure	TiSa	_ (CW)	2.5	800	85	C + GNR 5% (L)	0	intact	(3) 26.10	(3) 20.48	(3) 392.30#	(3) 164.24#	–
Mushaben et al., 2018 [36]	pig (EX)	tissue bonding + incision closure	TiSa	–	2.33	800	75	C + GNR 5% (L)	0	intact	(3) ~26	(3) ~18.5	(3) ~271.5#	(3) ~127#	–
Urie et al., 2018 [47]	pig (EX)	incision closure	TiSa	_ (CW)	6.4	800	72	MS + GNR (L)	0	intact	–	–	(6) 196.51#	(6) 155.66#	–
								C + GNR (L)		intact	–	–	(6) 196.51#	(6) 144.80#	–

Table 1B
LTS of the esophagus, stomach, colon and appendix.

Study	General Information		Laser					Solder	Outcomes						
	Model (Set Up)	Procedure	Type	power W (Mode)	Power Density W/cm^2	Wave-length nm	Heat C°	Composition (State of Matter)	Days from procedure	Control	Tensile Strength, (n) KPa		Burst Pressure, (n) mmHg		Micro
											Control	Intervention	Control	Intervention	
Esophagus															
Auteri et al., 1992 [42]	dog (IN)	incision reinforcement	diode	0.3 (CW)	9.6	808	–	HA 0.4 ml + AL 25% 0.2 ml + 3 drops ICG (L)	0	sutures	–	–	(10) 105*	(10) 251*	HPS
									2		–	–	(5) 121*	(5) 296*	
									7		–	–	(5) 197*	(5) 318*	
Nageris et al., 2004 [61]	rat (IN)	incision closure	CO2	_ (CW)	10	1060	70	BSA 50% (L)	14–42	sutures	–	–	–	–	H&E
Bleier et al., 2008 [62]	rabbit (EX)	incision reinforcement endoscopic closure	diode	0.5 (PW)	15.9	808	–	BSA 17% + ICG 0.5 mg/ml + HA sodium 4 mg/ml (L)	0	sutures	–	–	(5) 37.18*	(5) 71.6*	–
											–	–	(5) 37.18	(5) 54.78	H&E
Gabay et al., 2011 [32]	pig (EX)	incision closure	CO2	0.7 (–)	–	1060	60	AL 44% (L)	0	sutures	–	–	(?)	(20)	–
			GaAs diode	4.5 (–)	–	828		AL + ICG (SF)					73.55#	264.79#	
Abergel et al., 2011 [41]	pig (EX)	incision closure	CO2	_ (–)	–	1060	60	AL 44% (L)	0	sutures	–	–	(6)	(15)	–
			GaAs diode	_ (–)	–	830		AL + ICG (S/L)					77.96*#	264.06*#	
Stomach															
Bleustein, Cuomo et al., 2000 [63]	dog (IN)	bonding to bladder	diode	0.62 (CW)	–	1900	70	HSA 50% (L)	4	sutures	(9) ~20#	(9) ~40*#	–	–	H&E + Masson
									14		(9) ~400#	(6) ~450*#	–	–	
			Nd:YAG	2.8 (CW)	–	1320			4		(9) ~20#	(6) ~80#	–	–	
									14		(9) ~400#	(6) ~240#	–	–	
Bogni et al., 2012 [64]	pig (EX)	incision closure	diode	2.9 (–)	14.8	808	–	BSA 40% + ICG 0.1% (L) + plug	0	sutures	–	–	(10) 229*	(20) 416*	H&E
		acid incision closure endoscopic closure							0	sutures	–	–	(10) 229*	(20) 410*	
									0	–	–	–	–	(9) -	
Colon/Appendix															
Libutti et al., 1990 [65]	dog (IN)	anastomosis reinforcement	GaAlAs diode	0.37 (CW)	11.8	808	–	HF + ICG (L)	0	sutures	–	–	(8) 137*	(8) 326*	HPS
Moazami et al., 1990 [45]	rabbit (IN)	anastomosis reinforcement	diode	0.37 (CW)	4.8	808	–	HF + ICG (L)	0	sutures	–	–	(7) 108*	(6) 173*	HPS + Masson

Legend for Table 1A+B.

Set Up		Composition	
EX	Ex-vivo	AA	Acetic acid
IN	In-vivo	AL	Albumin
Mode		BSA	Bovine serum albumin
CW	Continuous wave	C	Collagen
PW	Pulsed wave	CB	Carbon clack
Tensile Strength/Burst Pressure		CH	Chitosan
*	Significant difference	ELP	Elastin-like polypeptide
#	Modified value	FFA	Free fatty acids
~	Data from a graph/diagram	G	Genipin
Micro		GNR	Gold nanorods
H&E	Hematoxylin & eosin	HA	Hyaluronic acid
HPS	Hematoxylin phloxine saffron	HF	Human fibrinogen
SEM	Scanning electron microscope	HPMC	Hydroxypropylmethylcellulose
TEM	Transmission electron microscopy	HSA	Human serum albumin
State of Matter		ICG	Indocyanine green
L	Liquid	MS	Methanol-treated silk
SF	Solid film	PCAPPS	Porcine concentrated autologous plasma protein solder
SS	Solid stent	SIS	Extra-cellular matrix from small intestine submucosa
S/L	Semisolid	V	Vancomycin

base for comparison between studies, we modified the values provided for the parameters of tensile strength, and burst pressure to units of KPa and mmHg, respectively. For studies that failed to provide tissue thickness (required for calculation of tensile strength in KPa units) a value of 1 mm for small animals (i.e., rat, rabbit, mouse) and 2 mm for large animals (i.e., pig, sheep, dog), was assumed in accordance with the data provided in studies that did provide tissue thickness [32–40]. For conversion of mass (gram units) to force (Newton units), 1 Kg was considered as 10 N. For studies that used solid film solders, the values of tensile strength represent the shear strength required to separate the soldered film from the tissue. Information regarding laser penetration depth or Beer-Lambert law calculations was present only in two articles [32,41] and therefore not included in the data analysis.

3. Results

Our initial search yielded 7622 potential results. Following removal of duplicates, we were left with 3731. Screening of titles and

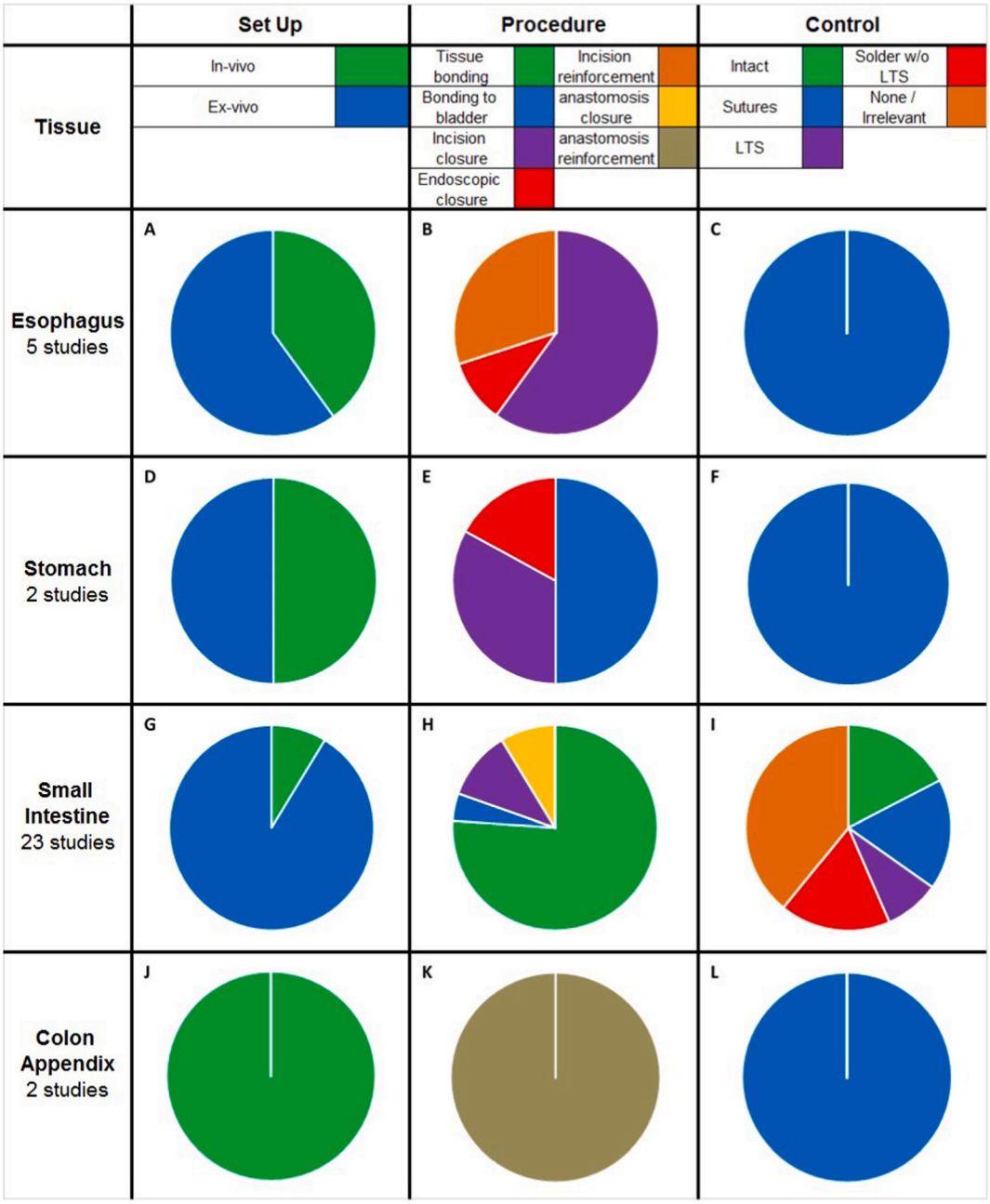

Fig. 2. Graphic representation of included study parameters.

abstracts generated 64 records, 39 of which were removed during full-text screening (38 articles did not meet the inclusion criteria and another one used data that was already presented in a different study). Manual screening of references of the remaining 25 provided 7 additional articles [34,42–47] for a total of 32. The selection process is depicted in Fig. 1. Risk of bias assessment resulted in no further eliminations. The complete scoring regarding risk of bias assessment for each article is available in supplementary figure 4. A total of 32 articles were included in the final data analysis and review. Of these, 23 involved soldering of the small intestine (Table 1A), 5 esophagus, 2 stomach, and 2 of the colon (Table 1B). A summary of the collected data is available in Table 1 (A + B) and the essential trends are depicted in Fig. 2. The majority (26 out of 32) of the reviewed experiments were performed using large animal models.

The lasers were activated in a continuous wave mode in nearly all the studies in which the operation mode was given (24 out of 27). Continuous wave mode enables continuous energy transfer and therefore, continuous heating. In the majority of experiments, 24 out of 32, the lasers emitted radiation in wavelengths of approximately 808 nm. This provided the penetration depth of 2 mm required for the soldering of tissues as thick as the intestinal wall of large animals [40]. Lasers with a lower penetration depth were utilized in some cases for soldering the superficial surface of the interface between the tissues [32,41]. Soldering temperatures were measured or reported only in part of the studies (17/32), and in most of those reported, it was determined to be around 65 °C. Importantly, while most studies measured the temperature on the tissue's external surface, at the location of laser irradiation, some also measured the value on the other side (inside the lumen). Naturally, there was a difference, as the light, as well as the heating, is applied from outside, and some studies attempted to address this issue to minimize it [33].

Regarding solder composition, the most common proteinaceous component in use was albumin (21 out of 32). Albumin undergoes denaturation following laser exposure, forming links with native tissue structure proteins providing both strength and water tightness until eventually replaced with new tissue by the body. In all studies from 2005 or later, a chromophore was added to the solution. Chromophores absorb light in certain wavelengths better than the surrounding tissues, enabling heating of the solder while maintaining a relatively low tissue temperature. Indocyanine green was the most frequent chromophore utilized (17 studies), while others used gold nanorods (5 studies). Seventeen of thirty studies prepared the solder as a dense, liquid paste. The paste was then smeared or manually dripped on the desired area using an applicator or pipette. The remaining studies transformed the liquid solder into a solid thin film by means of dehydration or compression. The films could then be applied to the outer surface of tissues for LTS of the serosal layer [53], or be rolled into a cylinder shape and used as a stent, for LTS of the mucosal layer [41].

A variety of controls were used by the different studies. Some cases compared LTS to a suture control group [32,41], while others provided a number of control groups: ruptured, intact and sutured tissues [47]. In other articles, the control groups were the LTS procedures themselves, so the comparison of results to conventional bonding methods or to intact tissue was impossible [35,43]. In some cases, there was no control group, as only the outcomes of different interventions were presented [51].

Microscopic analysis was used for the visual demonstration of the interface between the irradiated solder and neighboring tissues. Out of 32 studies, 15 incorporated histological staining and light microscopy using H&E (hematoxylin and eosin), HPS (hematoxylin phloxine saffron) and Masson staining. When compared with sutures, where a foreign body reaction was identified around the stiches, LTS resulted in most cases in a decreased inflammatory reaction [42,46,63,61]. These findings were also valid when sutures were reinforced with LTS, the combination resulting in less inflammation than sutures alone [42].

Three studies were identified which performed in-vivo assessments [45,46,63]. It seems that the use of LTS instead of, or in addition to sutures reduced the incidence and the severity of obstructions or narrowing following the procedure (most likely as the result of decreased local inflammatory reactions). Bleustein, Cuomo et al. [63] demonstrated a higher leak rate using a 1320 nm wave-length laser, compared to sutures or a 1900 nm laser, emphasizing the importance of the appropriate LTS for different tissue properties. Although most of the teams performed ex-vivo experiments, some evaluated longer term ramifications of LTS. Lauto et al. [56] tested the cytotoxicity of the solder over 48 h (in this particular trial, a negligible cytotoxic effect was reported) and Huang et al. [60] examined the impermeability of repaired tissues by monitoring the infiltration of bacteria through them.

3.1. LTS of the esophagus

Compared to other tissues of the gastrointestinal tract, the esophagus is unique in that it lacks the presence of an external serosa layer. Esophageal anastomoses are exceptionally prone to failure, as reflected by a high leak rate [63]. Five studies were found that examined esophageal tissue. Two used a porcine model, 1 on a dog, 1 on a rabbit and 1 on a rat. There was no data regarding tensile strength, as all the studies provided only burst strength. The most promising results were achieved by Gabay et al. [32] which demonstrated a burst pressure of 264 mmHg, in comparison with only 73 mmHg for sutures. Using a multi-wavelength laser, they heated the solder across the whole thickness of the tissue. Another interesting study by Bleier et al. [62] performed LTS via an endoscopic approach, which also yielded superior burst pressures compared to sutures. Earlier studies attempted to use LTS in the esophagus, not as a tissue bonding technique alone, but as a reinforcement to conventional sutures. Auteri et al. [42] demonstrated a consistent increase in burst pressures of sutures reinforced with LTS, compared with sutures alone, commencing immediately following the procedure and through the first week.

3.2. LTS of the stomach

Two studies investigated LTS on the stomach. Bleustein, Cuomo et al. [63] tested gastrocystoplasty (enlargement of the urinary bladder, using a graft of gastric tissue) in-vivo. The bonding between the two different tissues generated by LTS appeared to be at least as strong as sutures. A more recent study performed by Bogni et al. [64], demonstrated different variations of gastric LTS. They performed the LTS on unique testing conditions mimicking the acidic environment in the stomach and demonstrated a nearly doubled

burst pressure, compared to sutures. In addition, they attempted an endoscopic approach, and although quantitative measurements were not conducted, the integrity of the closure was confirmed by inflation.

3.3. LTS of the small intestine

As mentioned previously, 23 out of 32 studies performed LTS of the small intestine. Regardless of the relatively large number of publications, the procedure performed in most of the studies was tissue bonding (19 out of 23), compared to the more clinically relevant full circumferential anastomosis or even incision repair.

Spector et al. [37] used an albumin stent in combination with an albumin liquid solder to ensure a full thickness bond of the intestinal wall for the purpose of intestinal anastomosis. They demonstrated that compared with sutures, an anastomosis using LTS tolerated dramatically higher pressures (170 ± 40 compared to 83 ± 37). An innovative trend in recent years has been the introduction of solders containing novel gold nanorods, which have the potential to absorb and convey heat better than their traditional counterparts (i.e., albumin, chitosan) [36,38,47,60]. Use of such solders demonstrated an increase in burst pressures when compared with conventional sutures [47]. Foster et al. [43] performed an experiment in which antibiotics were added to the solder to locally convey antibiotics to the region, in addition to tissue bonding. Only one in-vivo study was performed on rabbit small intestine, which underwent an intestinal anastomosis that was examined after two weeks of healing [46]. Although it did not provide any measurements of force or pressure, the study gave a histological and clinical comparison between anastomoses using LTS and sutures. LTS anastomosis was less likely to cause obstructions or narrowing, in addition to decreased inflammation.

3.4. LTS of the colon and the appendix

A single study attempted to implement LTS in the colon. Performed by Libutti et al. [65], the relatively early experiment aimed to reinforce an anastomosis initially made using sutures. The addition of LTS increased burst pressure by more than double. Another study performed a similar procedure of suture reinforcement with LTS in appendicular tissue in-vivo [45]. The follow up lasted for a maximum of 30 days, with the animals sacrificed every two days for the first week, providing an ongoing comparison. In this study the reinforcement of sutures with LTS resulted in an immediate, significant increase in burst pressure, but this gap narrowed quickly and became insignificant. It is possible that data from larger groups would have resulted in the conclusion that reinforcement with LTS is beneficial not only for the establishment of a stronger immediate bonding, but also for the maintenance of the bond during the healing process. Importantly, implementation of LTS reduced the severity of obstruction (same overall rate of obstructive symptoms but more partial than complete obstructions) when they occurred.

4. Discussion

This is the first systematic review published on the subject of LTS and the gastrointestinal tract. A total of 32 articles were included in the final analysis. Most studies were conducted on large animal tissues, using liquid proteinaceous solder, and irradiated by a continuous wave laser at approximately 808 nm. The most common method for outcome evaluation was the measurement of tensile strength, in accordance with the prevalent procedure, bonding of tissue sections.

The strength of the bond is influenced by inclusion of the LTS process across as much of the tissue thickness as possible, as shown in various tissues [32,37,41]. This goal can be achieved by the use of proper components (i.e., laser and solder). The laser should be able to provide an adequate penetration depth. A wavelength of around 808 nm seems to provide the best results, at least in the esophagus and small intestine. However, it is important to note that although this wavelength provided the best results, only two studies provided objective data regarding penetration depth [32,41], and further studies may increase our knowledge regarding the best wavelength to use.

Soldering temperatures that were around 65 °C in almost all of the studies that reported them. This temperature enables protein denaturation that facilitates solder tissue bonding but also causes minimal thermal damage. The most common temperature measurement method was an IR thermometer coupled to the laser. Other methods, not laser-coupled, were an IR camera recording the surface temperature [36,47] and a thermocouple, either beneath the tissue [38] or between the tissue and the solder [43,44,53,56]. This temperature range is consistent with published data of laser tissue soldering of other tissues as well [6,66–68]. One study, Rabi et al., 2010 [59], demonstrated increasing bond strength with a series of rising temperatures up to 150 °C. Although they succeeded in providing bonding, this was an ex vivo study that measured only immediate bond strength and did not look at tissue damage. In an in vivo environment one would expect delayed failure from tissue necrosis.

The solder should be applied throughout the depth of the tissue edge to achieve maximum bonding area and therefore, strength. It must also effectively react with the laser. This can be accomplished by the traits of the proteinaceous component itself, as well as by using a chromophore, suitable to the wavelength of the laser (e.g., indocyanine green is a chromophore that reacts to light in wavelengths of 808 nm). The addition of a chromophore may also be beneficial to the reduction of the energy that is required to heat the solder to the target temperature, and thermal damage to adjacent tissues. The goal of reaching a maximal bonding area was implemented in various ways, among them the use of multi wave-length lasers [32,41].

Solders in different states of matter have been examined. Although some studies using solid films demonstrated promising outcomes, none of them were compared with sutures or intact tissue. Liquid solders were tested in a more controlled manner, and we find them to hold greater potential. As a non-contact method, LTS constitutes a conceptual progress, relative to conventional bonding techniques. But this advantage is not fully manifested as long as the solder application process is not contact-free as well. Attempts to

address this issue using microjets have been conducted in tissues other than the gastrointestinal tract [69]. Liquid solders are presumed to facilitate non-contact application better than solid ones. In addition, liquid solders may act as carriers for the purpose of local delivery of different agents. This idea has been applied by Foster et al., as described above [43] for local antibiotic delivery. This concept may be implemented for the administration of variety of different medications, other than antibiotics, such as analgesics or anti-inflammatory medications.

The success of LTS procedures depends on the adherence to a range of optimal proven settings. It is only natural that automated and computerized systems should be incorporated in it. Rabi et al., 2010 [59], included in the review, used a thermal feedback control system. Future development to advance the LTS of the GI tract should continue to develop thermal feedback controls, as well as implement laser distance measurement and image analysis providing superior bonding due to the controlled environment. Development of non-contact methods for solder application may make the requirement for manual handling of the tissue obsolete, and thus, promote the use of other technologies. The use of robot and laparoscopic assisted surgery is challenging and is limited in part by the long training needed to master it. Reduction of the need for short precise maneuvers may shorten and simplify some of these procedures. This was demonstrated in a recent study using a mouse skin model. In this case the laser components were operated robotically, while the solder was applied manually [15,16].

When compared with surgery, endoscopic approaches are less invasive, and frequently result in shorter recovery times and less complications. Endoscopic closure can have great potential in avoiding the morbidity of surgery. Two studies attempted to endoscopically close incisions by means of LTS, one in the esophagus and one in the stomach [62,64]. The results of these studies are encouraging and suggestive of potential, as their closures withstood pressures comparable to sutures [62], and were airtight [64].

5. Conclusions

The use of lasers, whether by welding or soldering, has gained attention in recent decades. Although the promise of quick, efficient, and automated tissue bonding has been around for some time, this field hasn't progressed as quickly as one might expect. Most studies are still carried out in laboratories, with only a few conducted in-vivo. One of the main obstacles facing future researchers and developers is the complexity of these systems and the number of parameters to optimize, which this review attempts to address. In addition, current traditional, cheap, and widely used methods of tissue bonding also inhibit the use of LTS. For this reason and with the hope of advancing this field we recommend adding LTS rather than attempting to completely replace current methods.

LTS has the potential to provide better sealing and burst pressure than conventional methods. Even though practiced mostly in early studies, the application of LTS on top of or in addition to sutures showed an impressive increase in burst pressures [42,45,62,65]. Histological findings of numerous studies revealed that LTS may decrease the inflammatory and foreign body reaction caused by sutures. Given these insights, we believe it may be beneficial and productive to reinforce conventional bonding with LTS in certain procedures. This may be done endoscopically or externally as a prevention measure as part of the original surgery. LTS is aimed to be a uniform intervention, evenly applied on a defined area. Thus, if added, it may decrease the rate of human errors in current conventional, manual tissue bonding methods, in addition to the proven increase in burst pressure, regardless of mistakes [42].

Our systematic review suggests that the best current use of LTS is for suture reinforcement and improved sealing of the anastomosis site. The recommended characteristics known thus far are using an 808 nm laser to create an adequate penetration depth and applying a liquid proteinaceous solder in a non-contact method, with an addition of indocyanine green as a chromophore, heating to a temperature of 65 °C, thus creating a maximal bonding area while avoiding thermal damage. We would recommend a laser-coupled system, together with another temperature meter as a backup and validation, as the most credible method for temperature measurement. Yet, the challenges are not all solved. Creating a unified soldering on an uneven surface, avoiding collateral damage for nearby tissues and organs, and a better understanding of the exact parameters for the best use of laser and solder are some of the questions that still need answers. Although the majority of experiments were conducted ex-vivo, LTS following further investigation and streamlining, has strong potential to be applied in a clinical setting as an adjunct or replacement of current technologies in the anastomosis and closure of gastrointestinal structures.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2023.e16018.

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