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A Randomised Clinical Trial of Buffered Tumescent Local Anaesthesia During Endothermal Ablation for Superficial Venous Incompetence

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WHAT THIS PAPER ADDS

This study demonstrates that the adjustment of the tumescent local anaesthesia (TLA) constituents can result in a significant reduction in pain experienced by the patient. The addition of $NaHCO_3$ is a simple and cost-effective method of optimising the patient experience by buffering the acidic pH. The outcomes of this study are likely to influence the wider practice of endovenous thermal ablation for the better and may slow the drive for a non-tumescent procedure. The study group has adopted this formulation as its "gold standard" TLA preparation.

Objective/background: Endovenous thermal ablation (EVTA) is the recommended first line intervention for superficial venous incompetence (SVI). While the infiltration of perivenous tumescent local anaesthesia (TLA) is key to procedural success, it is paradoxically the predominant source of patient reported discomfort. This randomised controlled trial investigates the potential to reduce peri-procedural pain and improve patient reported outcome measures (PROMs), including quality of life (QoL) using TLA buffered to physiological pH.

Methods: Patients undergoing great saphenous vein EVTA with concomitant phlebectomies were randomised to either standard (ST) or buffered (BT) TLA. Follow up assessments were performed at weeks 1, 6, and 12. The primary outcome was patient reported peri-procedural pain on a 100 mm visual analogue scale (VAS). Secondary outcomes were one week post-procedural pain VAS and analgesia use, QoL (disease specific: Aberdeen Varicose Vein Questionnaire [AVVQ]; generic: Short Form-36 [SF-36] and EuroQol 5 Dimensions Questionnaire [EQ-5D]), patient satisfaction VAS, technical success on duplex ultrasound (DUS) examination, and complications.

Results: Ninety-seven patients were randomised: 50 to ST and 47 to BT. The groups had comparable baseline demographics, Clinical Etiologic Anatomic Pathological, Venous Clinical Severity Score, QoL, and DUS parameters. Equally, intra-procedural parameters (volume of TLA, length of ablation, and linear energy delivered) were also comparable. Peri-procedural pain scores were significantly lower in the BT group with a mean $\pm$ SD score of 2.86 $\pm$ 3.57 versus 4.44 $\pm$ 2.94 ($p = .001$). Pain scores and analgesia use over the subsequent week were equivalent. SF-36 Bodily Pain domain scores were significantly better in the BT group at week 1 (77 vs. 62; $p = .008$). AVVQ, SF-36, and EQ-5D scores were otherwise similar between the groups throughout follow up, significantly improving over baseline. Technical success was high in both groups, with no major complications and few minor complications.

Conclusion: Buffered TLA offers a significantly lower peri-procedural pain experience for patients undergoing EVTA and should replace current tumescent formulae.

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INTRODUCTION

Endovenous thermal ablation (EVTA) is the recommended first line intervention for symptomatic superficial venous incompetence (SVI).[1,2] Numerous studies have demonstrated the short-term superiority of this modality, comprising both endovenous laser ablation (EVLA) and radiofrequency ablation (RFA), over conventional surgery in terms of quicker recovery, technical efficacy, and patient reported outcome measures (PROMs) including pain, satisfaction, and quality of life (QoL).[3–8]

Notwithstanding these proven benefits of EVTA over surgery, these techniques still have room for refinement, with the focus now turning to further improve patient experience, and clinical and cost-effectiveness.

An advantage of EVTA is that it can be easily performed under local anaesthetic (LA). A survey of patients with varicose veins has shown that two thirds would seek a LA procedure, given the option, and that treatment should be completed in one visit.[9]

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The infiltration of perivenous tumescent LA (TLA) is key to the technical success of EVTA by providing anaesthetic hydrodissection of surrounding soft tissue and nerves away from the vein, acting as a heat sink to protect surrounding tissues and placing the intima in closer proximity to the heat source via venous compression.

It is apparent from the literature that the constituents of TLA can vary greatly, and are often unreported, despite it being key to the success of the procedure. A typical solution consists of crystalloid containing dilute LA and epinephrine. Experience within the authors' institution has revealed that patients commonly report significant discomfort during the infiltration of TLA, and that changing the constituents of the solution appears to have an impact on the tolerability of its infiltration. Fundamentally, off the shelf LA solutions are acidic in nature, which is thought to be the primary explanation for the "stinging" pain associated with infiltration.

Previous non-venous studies have shown that buffering acidic LA solutions to a physiological pH can reduce the pain of infiltration; a Cochrane review revealed that adjustment of the pH of lidocaine solutions by the addition of sodium bicarbonate resulted in a significant reduction in patient reported pain on a 10 cm visual analogue scale (VAS) during skin infiltration.[10] This effect was greater with epinephrine containing solutions. Although this use of sodium bicarbonate to buffer local anaesthetic is technically "off label", it is supported worldwide in other applications.[11–13]

Given that the EVTA technique requires LA for both skin infiltration and for perivenous tumescence, it was hypothesised that the beneficial effects of a buffered solution could be even greater in this cohort of patients.

Through bench pH testing, an easily produced TLA solution with a physiological pH of between 7.35 and 7.45 has been reported.[14] A non-randomised cohort study of this solution has suggested significant merit in its improved tolerability of infiltration compared with its unbuffered form.

The aims of this randomised study were to compare periprocedural pain outcomes, during EVTA, between buffered and non-buffered TLA, and to assess any impact this may have on subsequent recovery, technical success, and QoL.

METHODS

Patients referred to a tertiary vascular surgery department with primary symptomatic SVI between October 2012 and May 2014 were assessed for participation in this randomised, single blinded, clinical trial of an investigational medicinal product. Authorisations were secured from the Medicines and Healthcare products Regulatory Agency and research ethics committee; it is registered on the European Union Clinical Trials Register (EudraCT 2011-005575-16).

Patients were seen in a dedicated one stop venous clinic where they underwent detailed clinical and duplex ultrasound (DUS) assessment as per UIP consensus guidelines,[15] which specify a complete assessment of the deep and superficial venous system to fully characterise the underlying anatomy and physiology. DUS examinations were performed by experienced individuals with a formal postgraduate vascular ultrasound qualification. Study inclusion criteria specified patients with primary unilateral symptomatic superficial venous incompetence attributable to saphenofemoral junction (SFJ) and great saphenous vein (GSV) reflux on DUS examination; incompetence was defined as reflux of at least 1 s on spectral Doppler analysis. Patients meeting these criteria, with clinical grades C2—C6 of the Clinical Etiologic Anatomic Pathological (CEAP) classification system,[16] deemed suitable to undergo EVTA (either RFA or EVLA), were identified for trial inclusion.

Exclusion criteria were an alternative (non-GSV) axis of incompetence, bilateral disease, when EVTA was not deemed technically feasible, for patients unwilling or unable to consent or participate in the study or follow up, pregnancy or within 6 months postpartum, previous ipsilateral deep venous thrombosis (DVT), isolated deep venous incompetence, active or recent thrombophlebitis (within the last 6 weeks), previous ipsilateral varicose vein treatment, or known peripheral arterial disease with impalpable foot pulses and ankle brachial pressure index $< .8$.

Once eligibility was confirmed, patients were invited to participate and to provide written informed consent. Patients were randomised to receive EVTA with either standard non-buffered TLA (the control group) or buffered TLA (the intervention group). Randomisation was performed via a dedicated web based service (www.sealedenvelope.com) on a 1:1 ratio in random permuted blocks. Trial participants were blinded to their randomisation.

Baseline patient data, including demographics, Venous Clinical Severity Score (VCSS),[17] CEAP,[16] QoL (Aberdeen Varicose Vein Questionnaire [AVVQ], Short Form-36 [SF-36], and EuroQol 5 Dimensions Questionnaire [EQ-5D]),[18–21] and DUS parameters, were recorded.

Interventions

EVTA procedures were performed on a daycase outpatient basis in a clean operating theatre setting by three experienced venous surgeons who have performed a high volume of both EVTA modalities in routine practice. The operating surgeon undertaking the procedure did so as per usual practice, independent of the trial team, performing the clinical assessment, pre-procedural DUS, marking of varicosities, and undertaking the procedure. They were not aware of the treatment allocation. Patients were risk assessed for venous thromboembolism using a standard proforma widely used in UK National Health Service (NHS) practice,[22] and those deemed to be at high risk received a single pre-procedural prophylactic dose of subcutaneous low molecular weight heparin. In the standing position, patients underwent pre-operative DUS marking by the operating surgeon, who confirmed the axis to be ablated, marked the lowest point of axial reflux (site of access) and the varicosities to undergo phlebectomy. A member of the theatre team was assigned to attend to patients' needs, to ensure comfort and distraction was equivalent for all cases. A member of the trial team was present to complete the study case report forms, formulate the TLA solution (as

described below), and facilitate patient flow. After skin cleansing and sterile draping, and following LA to skin (1% lidocaine with 1:200,000 epinephrine, buffered with 8.4% sodium bicarbonate in a 10:1 ratio), the GSV was cannulated at the lowest point of reflux with ultrasound guidance in reverse Trendelenburg position. For EVLA, the Seldinger technique was used to place a laser catheter (AngioDynamics, Cambridge, UK) with the tip at the SFJ. In the case of RFA (Venefit, Medtronic, Minneapolis, MN, USA [formerly Closurefast, Covidien]) a similar technique was employed to place the tip of the RFA catheter at the SFJ via a short 7 Fr introducer sheath. Ultrasound guided perivenous TLA was administered in the Trendelenburg position using a pedal operated peristaltic pump (Nouvag DP-20; Nouvag, Goldach, Switzerland) along the axis of the vein at a target of 10 mL/cm.

TLA

The control solution was made as per the authors' standard currently used solution: 1 L bag .9% sodium chloride, 100 mL extracted to leave 900 mL, to which 100 mL 1% lidocaine with 1:200,000 epinephrine was added.

This therefore gave a solution of .1% lidocaine with 1:2,000,000 epinephrine. This tumescent solution is widely used in several applications in routine surgical and dermatological procedures, including EVTA.

The buffered (investigation) solution was made as for the control solution above, with the addition of 10 mL 8.4% sodium bicarbonate.

EVLA employed a gold jacket tipped laser fibre (NeverTouch) delivering a 1470 nm 10 W continuous beam at a target Linear Endovenous Energy Density of 50—70 J/cm. RFA was performed in line with the manufacturer's recommendations, with two treatment cycles delivered to the proximal segment, then a single cycle was used for each segment in the remaining vein.

Ambulatory phlebectomy of pre-marked varicosities was performed through 2—4 mm stab incisions, under the same TLA as axial EVTA. All phlebectomy sites were dressed with Steri Strips, cotton wool, and gauze, and an elasticated compression bandage applied from foot to groin to stay in place for one week. Patients with C6 disease (active venous ulceration) were put into four layer compression bandaging. Compression regimens were standardised and after week 1 bandages were exchanged for a graduated compression stocking (Class I; 20 mmHg at the ankle) for the next 5 weeks. Equivalent analgesic prescriptions were issued with 7 days of paracetamol 1 g (four times a day) and diclofenac 50 mg (three times a day). Patients were followed up at 1, 6, and 12 weeks post-procedure.

Outcomes

Primary outcome. The primary outcome was peri-procedural pain recorded independently by the patient on an unmarked 10 cm VAS pain scale (0 = no pain, 10 = worst pain imaginable) ascertained immediately upon completion of the procedure.

Secondary outcomes. A 24 h average 10 cm VAS pain diary and analgesic requirement diary was completed by the patient over the subsequent 6 days. Objective assessment of the severity of venous disease was recorded by means of VCSS. Technical success was defined as complete occlusion of the treated vein on DUS examination. Complications were recorded in accordance with the Society of Interventional Radiology Standards of Practice Committee Guidelines.[23]

The time to return to work and to normal activity was self reported by the patient along with VAS ratings for satisfaction with overall outcome and cosmesis at 12 weeks. QoL was assessed by disease specific (AVVQ) and generic (SF-36 and EQ-5D) instruments, completed independently by the participants at all time points.

Power calculation

Based on the primary outcome measure of peri-procedural pain, taking into account the previous cohort study and a minimum clinically important difference of 13 mm (95% confidence interval 10—17, SD 18.3) on 100 mm VAS,[14,24] forty-three patients per group were required to see this effect size with a power of 90% and alpha of .05. Target recruitment was therefore 50 patients per group to allow for 15% dropout.

Data handling and statistical analysis

Data were recorded in a dedicated database (Microsoft Access). Data were tested for normality. Normally distributed data are presented as mean ± SD, and significance testing performed with paired and unpaired Student *t* tests.

Non-normally distributed data are presented as median (interquartile range [IQR]) values with analysis using Mann—Whitney *U* test for unrelated samples and Wilcoxon signed rank test for paired data. Friedman test was used to analyse multiple related samples across the study interval. Categorical data were analysed by means of chi-square test or, if necessary, Fisher's exact test. Analysis was by the principle of intention to treat. All data were collected during the dedicated clinic follow up. Statistical analysis was performed using SPSS version 20 (IBM, Armonk, NY, USA). A p value $< .05$ was considered statistically significant for single comparisons; Bonferroni correction was performed for multiple intra-group comparisons of QoL measures over time, with the adjusted alpha level reported.

RESULTS

A total of 97 patients were randomised and received intervention as intended (Fig. 1). Baseline variables and treatment parameters were comparable between the groups (Tables 1 and 2).

Interventions

Comparable lengths of vein ablated (40.0 cm vs. 35.1 cm) and volumes of tumescent (464 mL vs. 455 mL) were used

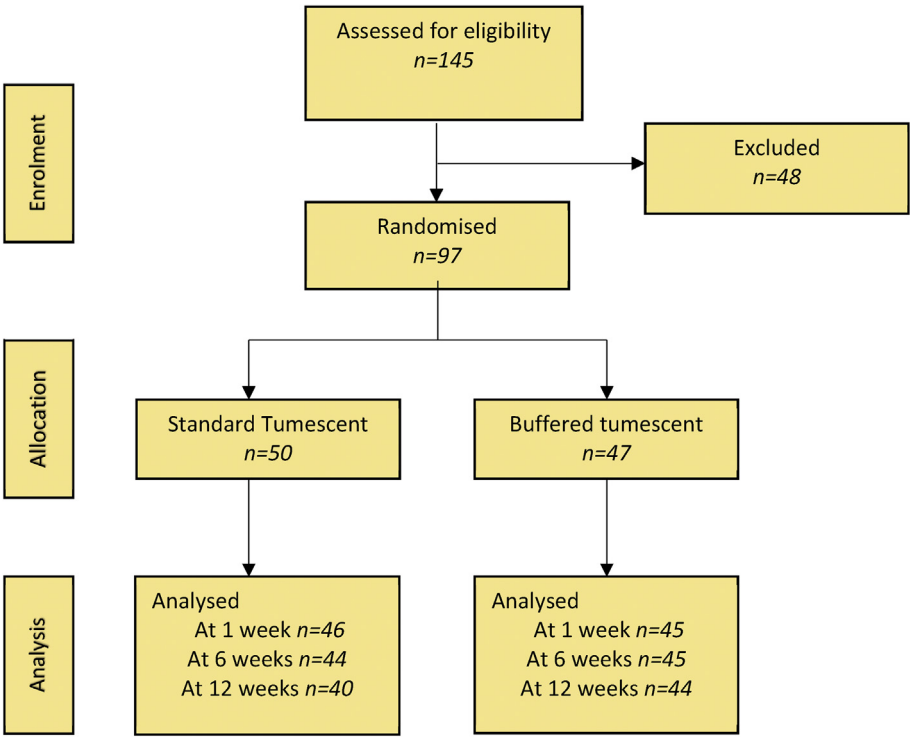

Figure 1. CONSORT diagram demonstrating participant flow through the study.

Table 1. The baseline comparison of the groups.

	Standard tumescent	Buffered tumescent	*p*
Mean ± SD age (y)	50.9 ± 15.7	48.5 ± 14.8	.277
Sex			.317
Male	20 (40)	16 (34)	
Female	30 (60)	31 (66)	
Mean ± SD height (cm)	173.1 ± 13.5	163.4 ± 22.1	.132
Mean ± SD weight (kg)	82.3 ± 16.7	82.4 ± 32.2	.987
Median (IQR) GSV diameter (cm)			
Groin	6.2 (5.2–6.9)	5.0 (4.3–8.0)	.387
Knee	5.1 (4.0–6.7)	5.4 (4.2–6.4)	.516
Median (IQR) VCSS	9 (6–12)	9 (6–12)	.570
CEAP (%)			
C2	27 (54)	24 (51)	.612
C3	10 (20)	13 (28)	.378
C4	11 (22)	7 (15)	.346
C5	2 (4)	2 (4)	.950
C6	0	1 (2)	.302
Median (IQR) AVVQ	13 (9.7–17.2)	13.8 (9.7–18.3)	.526
Median (IQR) SF-36 domains			
Physical Function	85 (73–98)	90 (75–95)	.700
Role-Physical	100 (50–100)	100 (75–100)	.564
Bodily Pain	100 (38–100)	62 (51–80)	.413
General Health	72 (62–85)	77 (62–87)	.255
Vitality	68 (48–80)	65 (50–80)	.848
Social Function	50 (50–94)	63 (50–88)	.400
Role-Emotional	100 (85–100)	100 (100–100)	.518
Mental Health	76 (62–90)	80 (64–88)	.956
EQ-5D Domain Index	.877 (.806–1)	.877 (.808–1)	.893

Note. Data are *n* (%) unless otherwise indicated. IQR = interquartile range; GSV = great saphenous vein; VCSS = Venous Clinical Severity Score; CEAP = Clinical Etiologic Anatomic Pathological; AVVQ = Aberdeen Varicose Vein Questionnaire; SF-36 = Short Form-36; EQ-5D = EuroQol 5 Dimensions Questionnaire.

Table 2. Interventional data.

	Standard tumescent	Buffered tumescent	*p*
EVLA: RFA	34: 16	33: 14	.815
Mean ± SD length of ablation (cm)	40.0 ± 16.2	35.1 ± 16.2	.207
Mean ± SD volume of tumescent (mL)	464 ± 163.8	455 ± 163.8	.843
EVLA			
Mean ± SD total Joules (J)	2141.9 ± 1097.1[a]	2124.8 ± 1322.0[b]	.954
Mean ± SD LEED (J/cm)	62.6 ± 13.1	65.4 ± 16.4	.499
Completion of procedure (%)	100	100	NA

Note. EVLA = endovenous laser ablation; RFA = radiofrequency ablation; LEED = linear endovenous energy density; NA = not applicable.
[a] Of 34.
[b] Of 33.

in each group (see Table 2). In both groups all patients underwent simultaneous phlebectomies.

Primary outcome: patient reported pain

There was a statistically significant difference in the immediate post-procedural pain scores. The buffered tumescent group recorded a median of 1.6 cm (IQR .8—3.1) versus the standard tumescent group score of 4.3 (IQR 2.3—6.1; $p = .001$ [Fig. 2]).

Secondary outcomes

Subsequent PROMs. Pain scores over the subsequent 6 days following treatment became equivalent with no statistical difference in pain scores between the two groups (see Fig. 2).

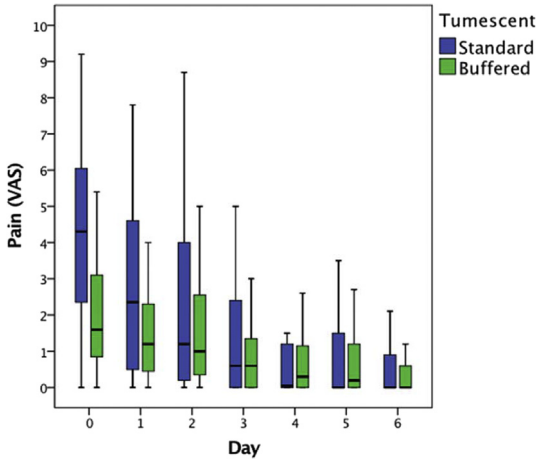

Figure 2. Post-procedural visual analogue scale (VAS) pain scores from day 0 (immediately post-treatment) to day 6. Immediate post-procedural (day 0) 1.6 cm buffered tumescent vs. 4.3 standard tumescent ($p = .001$).

Analgesia usage. Analgesia usage recorded over the post-operative period was also equivalent. There was no preponderance in either group for either paracetamol or ibuprofen usage (see Table 3).

Clinical classification (VCSS)

Both groups saw a significant improvement (decrease) in the VCSS scores over the study period from 9 (IQR 6—12) to 0 (IQR 0—0) ($p < .001$). There was no difference between the groups at any time point.

Complications

There were no incidences of DVT, allergy, infection, or haematoma. There was one episode of superficial thrombophlebitis in the standard group and equivalent rates of sensory disturbance (1 case at 12 weeks [2.1%]). A single patient on warfarin was seen for non-life threatening bleeding within the first 24 h of surgery; this was in the non-buffered group and required re-dressing only. There were no cases of LA toxicity.

Recovery

Return to normal activity was equivalent with the standard group having a median of 3 (IQR 1—4) days and the buffered group 2 (IQR 2—5; $p = .446$).

QoL outcomes

Disease specific QoL. The AVVQ scores detailed in Table 4 highlight that there was no detectable difference

Table 3. Percentage of patients taking paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) to control their pain.

Day	Paracetamol usage (%)			NSAID usage (%)		
	Standard ($n = 46$)	Buffered ($n = 45$)	*p*	Standard ($n = 46$)	Buffered ($n = 45$)	*p*
0	35.4	39.6	.440	37.5	35.45	.972
1	33.3	16.7	.830	29.2	35.4	.073
2	22.9	12.5	.388	31.3	18.8	.262
3	25.0	14.6	.586	29.2	14.6	.198
4	22.9	18.8	.983	22.9	16.7	.754
5	22.9	8.3	.096	20.8	16.7	.662
6	18.8	12.5	.699	14.6	8.3	.561

Table 4. Disease specific quality of life outcomes.

AVVQ	Standard	Buffered	*p*
Baseline	13.0 (9.7—17.2)	13.8 (9.7—18.3)	.526
Week 1	14.7 (11.5—20.2)	19.3 (14.2—23.1)	.054
Week 6	14.7 (11.5—20.2)	19.3 (13.5—22.9)	.084
Week 12	2.7 (0—7.6)	4.9 (2.0—10.8)	.151

Note. Data are median (interquartile range). AVVQ = Aberdeen Varicose Vein Questionnaire.

between the groups at any time point. There was an equivalent deterioration in both groups at week 1, but this was significantly improved compared with baseline at week 12.

Generic QoL. The buffered tumescent group demonstrated significantly higher (better) SF-36 Bodily Pain domain scores at week 1 with a median of 77 (IQR 62—87) versus 62 (IQR 41—74) in the control group ($p = .008$; see Fig. 3). Thereafter, there were no detectable differences between the groups at any time point (see Table 5).

Intra-group analysis of the buffered group confirmed a significant improvement over baseline in the Bodily Pain domain at week 1 ($p = .035$) and week 12 ($p = .005$; Bonferroni adjusted alpha = .025).

EQ-5D assessment revealed no difference between either group, with improvements over baseline in both groups at 12 weeks.

Patient satisfaction

Patients in both study groups were highly satisfied with the cosmetic outcome and treatment process with no variation between groups ($p > .05$).

Technical success

Both groups demonstrated comparably high rates of technical success at all time points (Table 6).

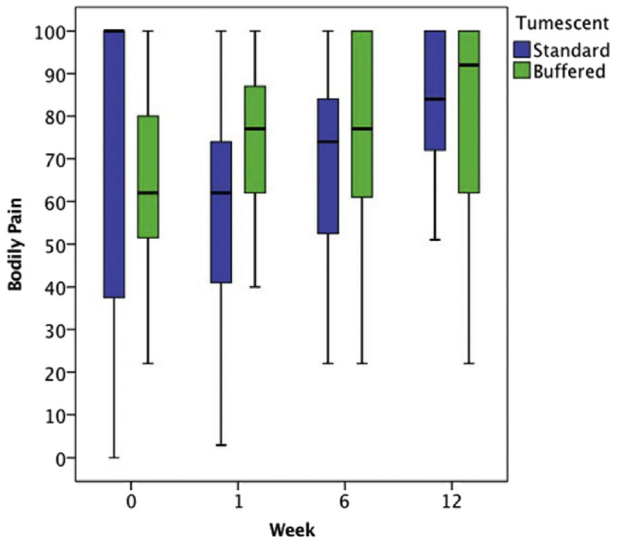

Figure 3. Bodily Pain (Short Form-36), over time, by tumescent group.

DISCUSSION

This study demonstrates that buffering TLA to physiological pH significantly reduces patient reported peri-operative pain, by a magnitude greater than the minimum clinically significant difference. While pain is associated with all invasive procedures, the aim is to reduce this to an acceptable level to improve PROMs without adversely affecting clinical or technical outcomes. The difference was short lived, only observed in the immediate peri-procedural scores, perhaps implying that the detected difference was due to the intervention alone. The comparable analgesic use between the groups during the following 6 days also implies that the short-term pain benefit during the procedure was due to the addition of sodium bicarbonate ($NaHCO_3$).

As mentioned previously, participants of other studies and anecdotal evidence of those receiving different manufacturer recipes for tumescence described a "stinging" or burning sensation when unbuffered tumescent was administered; this pain is often severe enough to deter patients from additional LA procedures.[11,25] The pain is associated with the high concentration of hydrogen ion ($[H^+]$) within the solution, which leads to an acidic pH.[26]

The concept of buffering the pH to reduce this pain by modulating the acidity was first described by McKay et al.[27] $NaHCO_3$ has been used in this manner in several medical and surgical procedures without complication or drug formula change.[13,28—33] The addition of $NaHCO_3$ to lidocaine alters the pH of the solution more than could be explained by simple dilution effect,[34] and this finding was also found in the Cochrane review.[10]

$NaHCO_3$ had been shown to increase the proportion of non-ionised lipid soluble LA. This reduces the time in which the LA crosses the cell membrane of the nerve fibre enhancing its rapidity,[12,35,36] without affecting the duration of action.[37]

It is well known that epinephrine acts as a vasoconstrictor and for this reason its inclusion in the TLA formula is key, particularly when performing concomitant ambulatory phlebectomy. The epinephrine allows higher dosages of lidocaine to be administered as it reduces the contact of the LA with the systemic circulation, through local vasoconstriction.

The pain scores found in the buffered group were significantly lower than the unbuffered control group. It is important to note that the control unbuffered tumescent group scores were 4.3 (IQR 2.3—6.1) with some comparability with other studies within the literature that quote VAS pain scores for EVTA procedures. An early ClosureFast study using unbuffered tumescent anaesthesia (50 mL saline with 20 mL 1% lidocaine with epinephrine) resulted in mean peri-procedural pain score of 4/10, with two fifths of all patients recording a VAS score > 4.[38] Pronk et al. found a mean $\pm$ SD VAS of pain during tumescent infiltration of 4.69 ± 2.48.[39] A ClosureFAST study that utilised buffered tumescent (1 L normal saline, 50 mL 1% Lidocaine, 1 mg epinephrine, and 10 mL 8.4% $NaHCO_3$) reported mean VAS scores of 3.1 (range 0—10) during the procedure.[40]

Table 5. Generic quality of life outcomes.

		Week	Standard	Buffered	*p*
SF-36	Physical Function	0	85 (73—98)	90 (75—95)	.700
		1	78 (60—95)	80 (70—90)	.891
		6	95 (85—100)	93 (68—100)	.428
		12	95 (75—100)	95 (70—100)	.640
	Role-Physical	0	100 (50—100)	100 (75—100)	.564
		1	75 (0—100)	75 (25—100)	.818
		6	100 (25—100)	100 (5—100)	.574
		12	100 (38—100)	100 (5—100)	.818
	Bodily Pain	0	100 (38—100)	62 (51—80)	.413
		1	62 (41—74)	77 (62—87)	**.008**
		6	74 (53—84)	77 (57—100)	.587
		12	84 (72—100)	92 (62—100)	.944
	General Health	0	72 (62—85)	77 (62—87)	.255
		1	71 (62—77)	62 (42—74)	.070
		6	72 (60—89)	77 (55—87)	.967
		12	72 (57—92)	75 (57—92)	.947
	Vitality	0	68 (48—80)	65 (45—80)	.848
		1	63 (45—75)	70 (50—80)	.964
		6	70 (55—85)	73 (50—80)	.780
		12	75 (55—90)	70 (50—85)	.634
	Social Function	0	50 (50—94)	63 (50—75)	.400
		1	50 (50—75)	50 (50—75)	.412
		6	50 (50—100)	56 (50—75)	.464
		12	75 (55—90)	70- (50—85)	.664
	Role- Emotional	0	100 (85—100)	100 (100—100)	.518
		1	100 (33—100)	100 (100—100)	.374
		6	100 (100—100)	100 (73—100)	.153
		12	100 (100—100)	100 (100—100)	.312
	Mental Health	0	76 (62—90)	80 (64—88)	.965
		1	80 (68—92)	80 (64—88)	.710
		6	84 (74—92)	84 (74—92)	.617
		12	88 (80—96)	86 (76—92)	.284
EQ-5D		0	.877 (.806—1.000)	.877 (.808—1.000)	.974
		1	.877 (772—1.000)	.824 (.701—.877)	.237
		6	.895 (.877—1.000)	1.000 (.701—1.000)	.992
		12	1.000 (.848—1.000)	1.000 (.833—1.000)	.914

Note. Data are median (IQR). Bold values are significant. SF-36 = Short Form-36; EQ-5D = EuroQol 5 Dimensions Questionnaire.

The buffered tumescent group reported lower scores than seen in previous studies and given that the effects were detected immediately post-procedure and not on subsequent days, suggests that the difference was attributable to the intervention alone.

An area highlighted as a potential confounder is the extent of simultaneous phlebectomies. These were performed for all participants in line with the authors' unit policy, as this has been proven to be superior in terms of QoL outcomes and reduced further treatment in two randomised controlled trial (RCTs).[41,42] The number of phlebectomies was not recorded; however, the view was taken that this was a pragmatic study, recruiting patients from an unselected routine NHS referral system and that through randomisation the extent of phlebectomies would be equivalent. Given the volume of TLA used, the lengths of ablation and the patient satisfaction scores were all comparable between the groups, it is reasonable to assume that the extent of phlebectomy was similar.

Table 6. Technical success.

Duplex occlusion	Standard	Buffered	*p*
Week 1	49/50 (98%)	46/47 (98%)	.988
Week 12	38/40 (95%)	43/44 (98%)	.495

Note. Data are *n* (%).

Clinical outcomes

The buffered tumescent did not have an adverse effect on VCSS scores, which were equivalent between the groups.

Comparable recovery time frames were seen indicating that any benefit on peri-procedural pain was short-lived and overall did not influence recovery.

Complications

There were no major complications (venous thromboembolism or nerve injury) and there were low rates of minor complications to a level comparable with other studies.[43]

Bruising was not assessed in this study as it is a highly subjective outcome measure that is open to reporting bias

and a lack of well validated assessment method with methods including photography and Likert scale.[7,44] The change in TLA was not expected to have any impact on bruising between the groups.

QoL outcomes

The differences in peri-procedural pain between the groups were not reflected in the disease specific assessment of QoL. Although not powered to specifically identify changes in QoL it is useful to highlight that there was no detrimental impact on the disease specific outcomes.

Conversely, however, there was a significant difference in the Bodily Pain domain of the SF-36 generic QoL assessment at week 1; the findings demonstrated a higher (better) score in the buffered group (median 77; IQR 62—87) versus the standard tumescent group (median 62; IQR 41—74; $p = .035$). Small modifications of technique such as this clearly have the potential to make modest, but significant, improvements in PROMs, which over time, when combined with other appropriate changes in technique and technology, may cumulatively result in a much greater impact.

The remaining SF-36 domains and the EQ-5D outcomes were similar in trends and outcomes with no differences between the groups over time but equal improvements from baseline. The findings in both the disease specific and generic QoL scores are seen in the wider literature.[45]

Alternative tumescent techniques

As described above, TLA is pivotal to the success of EVTA, while paradoxically influencing the patient reported pain outcomes significantly. Therefore, several other groups have investigated the effect of TLA modification to improve outcomes.

Saline alone has been used as a tumescent agent, without LA but cooled to 4 °C.[46]

This was a case series of 12 patients, with no objective assessment of pain, patient satisfaction, or QoL, and was used for axial EVLA ablation alone, not including phlebectomy. It is therefore difficult to draw any meaningful conclusion transferrable to clinical practice.

In this study, storage and infiltration of the TLA solution occurred at ambient room temperature (21—23 °C). This is an important consideration as acidic solutions tend to increase in pH with increasing temperature, while alkali solutions decrease in pH and neutral pH solutions tend to remain stable.[47] Warming the tumescent therefore increases the pH and would theoretically reduce the pain on infiltration. Several RCTs and a meta-analysis have supported this theory showing that infiltration of warmed LA appears to be better tolerated than cold or room temperature LA.[48—50] Pannier et al. conducted an RCT of cold (5 °C) versus warmed (37 °C) tumescent anaesthesia during 1470 nm EVLA.[51] Post-procedural pain on a VAS of 0—4 up to day 10 found a non-significant mean pain score on days 2—10 of 1.0 and 1.2, respectively.

An alternative to buffering would be to warm TLA to 37 °C adding impracticalities in the clinical environment requiring preparation, warming, and time. Warmed TLA would also have a reduced heat sink effect and may lead to tissue damage. There is no pH data for TLA at 37 °C; it may be that a smaller quantity of buffer is required. Equally, alternative crystalloid solutions may be used in lieu of .9% sodium chloride; to the authors' knowledge, no laboratory or clinical testing of other crystalloid solutions in TLA formulations has been reported. This RCT is the culmination of a unique programme of work aimed at identifying an easily produced, and clinically and cost-effective TLA for EVTA.

The new tumescent-less ablative treatments, such as mechano-chemical ablation and cyanoacrylate adhesive, offer an alternative ablative therapy without the need for TLA. However, these techniques currently only have short-term technical outcome data and do not address varicosities unless combined with phlebectomy or foam sclerotherapy, which may offset any benefit in improved pain outcomes. Therefore, there is no evidence to suggest the tumescent-less techniques will replace EVTA and hence it remains important to identify how EVTA can be further refined and optimised for both clinical outcomes and PROMs.

CONCLUSION

This study has demonstrated that a simple adjustment of the TLA constituents can result in significantly reduced peri-procedural pain experienced by the patient. The addition of $NaHCO_3$ did not cost on a clinical or patient level and, indeed, is a cheap and effective way of optimising the patient experience. The outcomes of this study are likely to influence the wider practice of endovenous thermal ablation for the better and may slow the drive for a tumescent-less procedure. The study group has adopted this formulation as its "gold standard" TLA preparation.

CONFLICT OF INTEREST

None.

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