

High Volume Liposuction in Tumescence Anesthesia in Lipedema Patients: A Retrospective Analysis

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ABSTRACT

Background: Lipedema is a chronic, progressive disease that occurs almost exclusively in women and leads to pathological, painful fat growths at the extremities. Only symptomatic therapy can be offered since the etiology of the disease has not yet been clarified. Liposuction in tumescent anesthesia has established itself as a surgical treatment method of choice. The complication rate associated with the procedure and the pharmacological course and safety of treatment in patients with lipedema has not yet been sufficiently studied. The aim of the study was to broaden the evidence on the safety of ambulatory high-volume liposuction in tumescent anesthesia in lipedema patients. Influencing factors of patients (weight, fat content, comorbidities) or the process technique (drug administration, volume of aspirates) should be investigated on the safety and risks of tumescent anesthesia. This was a retrospective data analysis in which data from 27 patients (40 liposuction procedures) treated at the Sandhofer and Barsch lipedema center between 2016 and 2018 were evaluated. The liposuctions were carried out in tumescent anesthesia and using a Power-Assisted Liposuction system. Clinical examinations and regular blood samples were carried out before the procedure, intra- and postoperatively. The procedures lasted an average of 118 minutes and an average of 6111 ml of aspirate was removed. For tumescent anesthesia, patients were given an average lidocaine dose of 34.23 mg/kg body weight and an epinephrine dose of 0.11 mg/kg body weight. No relevant complications associated with drug side effects, hypovolemia or hypervolemia or blood loss were detected. Liposuction under high volume tumescent anesthesia for the treatment of lipedema patients is, even for major intervention, a safe procedure.

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INTRODUCTION

Liposuction is one of the most common surgical procedures in aesthetic surgery worldwide and was first described in the mid-1990s as a therapy for lipedema.^{1,2} During this time, liposuction could be established as a safe and effective therapeutic alternative in the treatment of lipedema, especially by German, Austrian and Dutch operative dermatologists.³⁻⁹ Further development of the surgical procedure using lymph-friendly liposuction techniques with fine cannulas, liposuction has established itself as an important, minimally invasive therapeutic approach for lipedema.⁸ Several studies have shown that liposuction significantly reduced sensitivity to pain and pressure as well as the tendency to hematoma.¹⁰ Improving mobility after the procedure leads to an increase in energy turnover, which can contribute to further weight loss.⁸ Several studies describe a significant improvement in the quality of life due to the suction of the pathological fat tissue, which can still be demonstrated eight years after the intervention.^{10,11} To date a causal therapy for lipedema is not known. The treatment

of lipedema is based on conservative physical decongestive therapy and surgical liposuction of the pathological adipose tissue augmentation. The appropriate treatment method should be determined individually for each patient.¹² The excessive increase in adipose tissue and the resulting restrictions in mobility as well as the disproportionate appearance cannot be treated with conservative therapy,¹³ especially if there is no edema present. Manual lymphatic drainage (MLD), intermittent pneumatic compression, compression stockings, exercise, and skin care are often used to control pain and symptoms in lymphedema and therefore also in lipedema. Recent studies have shown that there is little or no lymphedema in lipedema.^{14,15} All over, the term lipedema is a misnomer, since more than 90% of typical lipedema patients do not have any edema. Especially the patients that are seen in the practice, in contrary to the patients seen in specialized lymph clinics, where the percentage of lipedema patients with an edema is a bit higher. Treatment with MLD showed no significant therapeutic effect

on lipedema apart from a short relief due to patients' care. In the contrary, seeing a few hundred lipedema patients a year in the Austrian lipedema center it is significant that a lot of lipedema patients report that the compression stocking aggravate pain in lipedema patients (own observation). Surgical treatment involves sensitive, atraumatic lymph-sparing liposuction using tumescent local anesthesia. The treatment has been proven to be safe and effective for cosmetic indications and lipedema.^{5,16-19} Tumescent anesthesia is a special form of local anesthesia, in which large amounts of an anesthetic solution, consisting of a physiological solution with local anesthetics and epinephrine, are introduced into the subcutaneous adipose tissue. This local anesthesia makes large areas of the skin insensitive to pain and surgical interventions can be carried out without an additional anesthetic procedure.^{20,21} In the early days of surgical liposuction, bleeding and the associated high need for transfusion was the limiting factor in liposuction. By adding epinephrine to the infiltration fluid, liposuction could be achieved without the need for a transfusion.²² Since nowadays high amount of fluid is used, the additional compression of the fluid on the vessels further decreases blood loss during intervention. Examination of adipose tissue using lymphoscintigraphy and immunohistochemistry after liposuction has demonstrated no significant damage to lymphatic vessels using tumescent local anesthesia compared with traditional liposuction techniques using general anesthesia. Liposuction techniques using radio frequency, ultrasound, or laser are not useful for lipedema patients because of possible damage to lymphatic vessels.¹³ The effectiveness of liposuction using tumescent anesthesia is based on the fact, that beside subtotal removal of fat, the capillaries, including the well-known leaky vessels in lipedema, can be removed. This results in no, or far less bruises for the patients after the liposuction and leads to the suppression of angiogenesis and subsequently adipogenesis at the cellular level.^{23,24} That explains the sustainable impact as described by Baumgartner and Schmeller.¹¹ Klein et al looked at the serum levels of the lidocaine on small liposuction volumes, with patients he injected tumescence solution and did not aspirate and patients he injected tumescence solution and performed a normal liposuction afterwards, resulting in lower lidocaine serum levels when he aspirated.²⁵ This is not comparable to lipedema since the liposuction volume of lipedema patients is extremely high. In general, a critical consideration regarding local tumescence anesthesia should be given in terms of large amounts of tumescence infiltrates, which could lead to hypervolemia or pulmonary edema. Removing large amounts of fat also creates the potential for hypovolemia (shock). The amount of local anesthetic and epinephrine can lead to toxic reactions.²⁵ There is also the fundamental question of whether liposuction should be performed under general or local anesthesia with slight analgesic sedation.²⁶ Necessarily, parameters such as blood loss, infection, and pain should be taken under consideration. An important point is the exact,

previous fat analysis with the impedance measurement, to classify a metabolic disorder, accurately determine the total amount of fat in the patient. Since lidocaine is a lipophilic substance, from the amount of total fat we can predict the appropriate lidocaine dose in tumescent solution. This method is also extremely helpful to control the postoperative course (weight and lifestyle). Jeffrey Klein published the first study on the use of tumescent anesthesia in 1987. The anesthetic solution described consisted of physiological saline (0.9% NaCl) with 0.091% lidocaine (910 mg/l) and 0.91 mg/l epinephrine.²⁰ Klein modified the recommendations for the composition of the anesthetic solution several times in subsequent studies. In 1999 he published that the concentrations of the substances dissolved in the anesthetic fluid should be made dependent on the region of the body to be treated.²⁷ To date, there are no guidelines specifying the exact composition of the infiltration solution. The lidocaine concentration used in the solution varies, depending on the surgeon, between 500–1500 mg/l and the epinephrine concentration between 0.5–1.5 mg / l.⁴ No data are available for large-volume liposuction, as it is the case with lipedema.

We are the first who examined lidocaine and epinephrine in serum after high volume liposuctions in lipedema. In the present study we analyzed the safety and efficacy of liposuction regarding different parameters. During the regular quality management, lidocaine and epinephrine levels were determined intra- and post-operatively and the clinical course was examined. In this retrospective data analysis, randomized data were selectively collected from 27 patients who underwent 40 liposuctions between 2016 and 2018, whereas 13 patients from this cohort underwent a second liposuction within 3 days.

MATERIALS AND METHODS

Liposuction Procedure

Depending on the severity of the lipedema, two or three procedures for the legs and one procedure for the arms, if affected, were planned for each patient. All interventions were performed under tumescent anesthesia and superficial sedoanalgesia, which was performed and monitored by an anesthetist. After premedication with midazolam 7.5 mg orally, the analgesia was carried out with 3–5 mg intravenous midazolam and continuous administration of low dose remifentanyl via a perfusor. In the case of marked anxiety, a further midazolam of 1–2 mg or 30–60 µg clonidine was administered if necessary. The patients were always responsive during liposuction and were able to independently change the position during the procedure and contract specific muscle groups if the surgeon asks for it. This is necessary for a better esthetic outcome and one of the major advantages of a sedoanalgesia compared to general anesthesia. The tumescent fluid was freshly prepared before the procedure and warmed to 37°C and introduced into the subcutaneous adipose tissue by 2 persons simultaneously

under pressure using a KMI Surgical Infusion/Irrigation Pump. The infiltration cannulas were wiped like a wiper, starting in the depth near the fascia and were then extended to the upper layers and continued until the infiltrated tissue developed a firm whitish skin turgor (state of tumescence). "Vivomed infiltration needles 1.2x100 mm" were used for infiltration. After a waiting period of 30 minutes, liposuction was started. Liposuction was carried out using the PAL Liposuction System from MicroAire. In order to make liposuction gentler, the suction cannula was set in motion. The cannulas with a diameter of 3 to 4 mm were inserted into the subcutaneous fat tissue via small incisions of approximately 4 mm. The suction was carried out considering the position and course of the lymphatic vessels. If pain is indicated intraoperatively, a minimal secondary infiltration is carried out with a blunt, 40 cm long infiltration cannula with a diameter of 2 mm. No intravenous fluid substitution was performed. All patients were only discharged when they met the discharge criteria.

Data Collection

A detailed medical history and a physical examination were carried out preoperatively to confirm the diagnosis of all patients. All patients were weighed using a body analyzer scale (impedance measurement) and the results regarding weight, body fat percentage and visceral fat, and BMI were recorded in the medical history. In addition, an electrocardiogram (EKG) examination was carried out to rule out cardiac problems. During the operation, the data on the amount of tumescent solution used and its composition was noted. A distinction was made between the infiltration phase and the actual liposuction. The amount of the aspirate and the fat content in the aspirate were documented. During the operation and postoperative care, the vital parameters (blood pressure, pulse, oxygen saturation) were collected and documented several times. This was done before and during the operation, as well as after 4, 8, 12, 16, 20, 28, and 44 hours after the procedure. All patients underwent blood sampling after infiltration and before liposuction, after liposuction and after 4, 8, 12, 16, 20, 28, and 44 hours. For further analysis, the samples were sent to the Institute for Clinical Chemistry at the University of Mannheim, where the lidocaine and epinephrine levels were determined. A blood count was determined from the first and the last sample in order to examine the drop-in hemoglobin and hematocrit level. Heart enzymes and liver function parameters were determined at the end of the operation and after 20 hours.

Side Effects

During the postoperative visits, the patients were asked about their well-being, exercise capacity and postoperative pain on the VAS scale (1–10). The information on the subjective assessment of side effects was divided into five categories. In addition, complications observed postoperatively (nausea, tinnitus, circulatory problems, rapid heartbeat, shortness of breath)

or additional medication administered were documented. The amount of oral fluid intake was recorded by the patients themselves. The survey was carried out analogously to the blood tests performed before the operation, after the operation, and after 4, 8, 12, 16, 20, 28, and 44 hours. In the course of the postoperative visits, the patients were asked to get up and walk a few rounds through the room.

Ultrasound Examination

Preoperatively we looked for venous disorders, the quality and structure of fat, exclusion of edemas (lymphedema, phlebedema, lipolymphedema, and lipophlebolymphedema), and the thickness of fat over the proximal and the distal tibia. In contrast to the hypoechoic structure of normal adipose tissue, lipedema appears widened with hyperechoic connective tissue septa and the typical image of a "snow storm pattern". In the case of an insufficient veins which needed to be treated, this was done at least 2 months before the liposuction. The thickness of the fat pretibial proximal and distal, the position of the small saphenous vein in the middle calf and the determination of the Marshall point as described elsewhere,²⁸ as well as the exclusion of lymphedema confirmed the diagnosis of lipedema (lipophobia of the tissue). A sonographic assessment of the pleural space, the inferior caval vein and the heart was carried out before the operation, at the end of the operation and after 20 hours post-surgery. It was recorded whether evidence of hypervolemia with pulmonary edema or hypovolemia could be found. During echocardiography, the ejection fraction was determined and whether wall movement disorders occurred.

Electrocardiography (ECG)

A 12-lead ECG examination was carried out several times on all patients. This was done before the operation, at the end of the operation and 20 hours after the procedure. To evaluate this retrospective data analysis, the existing ECGs were presented anonymously to an uninvolved cardiologist for evaluation. It was analyzed whether new ECG changes appeared.

RESULTS

General Data on Patient, Operation, and Medication

The study is a retrospective data analysis in which data from 27 patients were evaluated who underwent liposuction at the Sandhofer and Barsch Lipedema Center in 2016–2018. During the regular quality management, lidocaine and epinephrine levels were determined intra- and post-operatively by 27 patients and the clinical course was examined. According to the inclusion criteria, only these patients are used for the present data analysis. Only patients were included who had a complete record of the treatment including lidocaine and epinephrine levels, as well as post-operative clinical follow-up. Analyzing the treated patients master data revealed an average age of 41.7 years, body weight of 90.3 kg, and a height of 167.4 cm, which resulted in an average BMI of 32.3 (Table 1). Regarding the general operation data, the

TABLE 1.

Patient Master Data. The treated patients were on average 41.7 years old, weighted 90.3 kg and were 167.4 cm tall, which resulted in an average BMI of 32.3.

	Mean	σ
Age	41.7	12.7
Body weight [kg]	90.3	16.4
Body fat [kg]	35.4	10.6
Visceral fat [%]	8.3	3.1
Body height [cm]	167.4	5.3
BMI	32.3	5.9

TABLE 2.

General Operation Data. The procedure lasted an average of 118 minutes. An average of 6111 ml was aspirated, of which an average of 5585 ml was fat. During tumescent anesthesia, an average of 11,404 ml of anesthetic fluid was administered.

	Mean	σ
Operation time [min]	118	17.7
Aspirate [ml]	6111	2029
Fat in aspirate [ml]	5585	1932
TF volume admin. [ml]	11404	3067

TABLE 3.

Administered Medication Doses. Total amount of lidocaine was administered during the operation with an average dose of 3061.9 mg and 34.23 mg/kg body weight. In addition, an average of 9.7 mg epinephrine, corresponding to a dose of 0.11 mg / kg body weight, was administered during tumescent anesthesia.

	Mean	σ
Lidocaine total [mg]	3061.9	643.6
Lidocaine/kg bw [mg]	34.23	5.49
Epinephrine total [mg]	9.71	3.28
Epinephrine/kg bw [mg]	0.11	0.03

procedure lasted an average of 118 minutes where 6111 ml was aspirated, of which an average of 5585 ml was fat. The average anesthetic fluid administered during tumescent anesthesia was 11,404 ml (Table 2). The amount of lidocaine administered during the operation is 3061.9 mg and corresponds to a lidocaine dose of 34.23 mg/kg body weight. In addition, an average of 9.7 mg epinephrine, corresponding to a dose of 0.11 mg/kg body weight, was administered during tumescent anesthesia (Table 3).

Course of the Lidocaine Level

The lidocaine levels were measured regularly at defined times in all patients. During the course, an early peak after 4 hours at an average of 1.65 $\mu\text{g}/\text{ml}$ and a second peak after 16 hours at 1.55 $\mu\text{g}/\text{ml}$ could be determined. The mirror courses of the patients were very variable with high standard deviations. (Figure 1).

FIGURE 1. The average lidocaine levels of all patients after the procedure and 4, 8, 12, 16, 20, 28, and 44 hours later. Mean \pm SD. N=27.

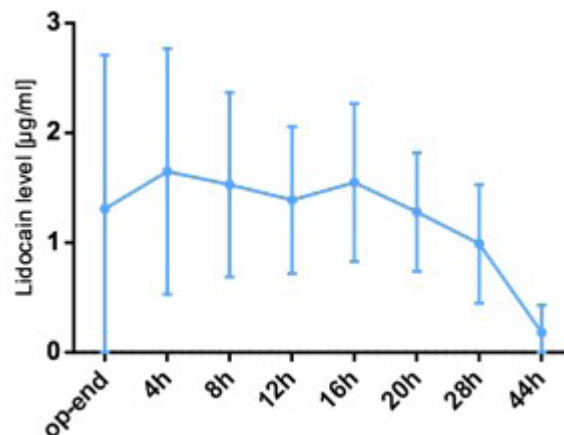
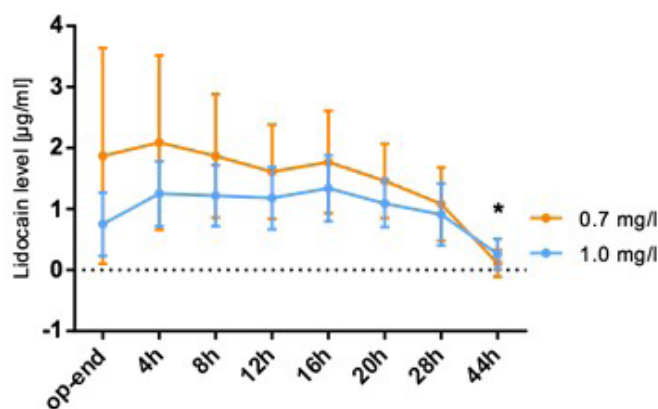


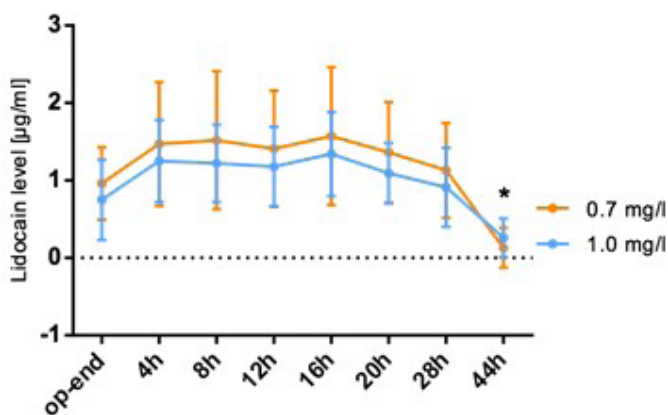
FIGURE 2. The average lidocaine levels separated according to the epinephrine concentration (0.7 and 1.0 mg/l) in the tumescent fluid after the procedure and 4, 8, 12, 16, 20, 28, and 44 hours later. Mean \pm SD. N=27. $P < 0.05$.



Influence of the Epinephrine Dose on the Course of the Lidocaine Level

The average lidocaine levels separated according to the epinephrine concentration in the tumescent fluid. The patients were divided into two groups according to the epinephrine concentration used in the tumescent fluid. In the group with 0.7 mg epinephrine per liter ($n = 14$), on average higher values could be measured up to 28 hours than in patients in whom a tumescent liquid with 1.0 mg epinephrine per liter was used. In both groups the bimodal course of the levels can be seen, which was also found in the total population. The differences in the mean lidocaine levels between the two groups were tested using a two-factor ANOVA with repeated measurements. After correction according to Greenhouse Geisser, there was a significant difference between the lidocaine levels of the two TF groups. ($P = 0.31$). In addition, the lidocaine levels were compared using the Mann-Whitney U test for each measurement time. However, due to the high standard deviations, this could not be detected, except at the end of the measurement after 44 hours. $P < 0.05$. (Figure 2).

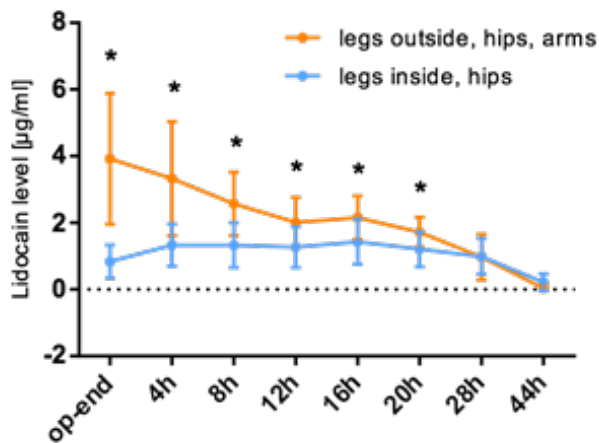
FIGURE 3. Influence of the epinephrine dose (0.7 and 1.0 mg/l) on the course of the lidocaine level (without arms) after the procedure and 4, 8, 12, 16, 20, 28, and 44 hours later. Mean \pm SD. N=27. $P<0.05$.



Influence of the Epinephrine Dose on the Course of the Lidocaine Level (Without Arms)

The average lidocaine levels of all patients who did not receive any treatment on the arms. After the exclusion, 13 patients remained in the group with 1.0 mg/l and 10 patients in the group with 0.7 mg/l epinephrine. The group with 0.7 mg/l epinephrine also shows higher values on average, but the difference between the two groups is significantly smaller. The course curves are almost parallel. When comparing the lidocaine levels using a two-factor ANOVA with repeated measurements, no significant difference between the two groups could be found after 4, 8, 12, 16, 20, and 28 hours ($P=0.556$) except after 44h ($P<0.05$; Figure 3).

FIGURE 4. Influence of the operating region on the course of the lidocaine level (+arms). The average lidocaine levels separated according to the treated body region (legs outside, hips and arms/ legs inside, and hips) measured after the procedure, 4, 8, 12, 16, 20, 28, and 44 hours later. Significant differences could be obtained after the procedure and 4, 8, 12, 16, and 20 hours later. Mean \pm SD. N=27. $P<0.05$.



Influence of the Operating Region on the Course of the Lidocaine Level (With Arms)

In patients who were operated on the arms ($n = 4$), high levels (3.92 $\mu\text{g/ml}$) could be measured at the end of the operation. In the first twelve hours there was a linear drop to an average of 2.01 $\mu\text{g/ml}$ and after 16 hours after a slight increase it reached 2.15 $\mu\text{g/ml}$ its second peak. Patients who underwent surgery on the legs and hips only ($n = 23$) showed lower levels on average over the first 28 hours. In contrast to the comparison group, these patients only reached their first peak after 4 hours to an average of 1.33 $\mu\text{g/ml}$ and fell only very slightly until they reached their maximum (1.43 $\mu\text{g/ml}$) after 16 hours. The lidocaine levels after the operation were compared with repeated measurements using two-way ANOVA. There was a significant difference during the lidocaine levels between the two groups ($P<0.05$). The reason for the high lidocaine levels in the arm region after liposuction is, that lidocaine diffuses into the cubital vein of the arm and can be therefore explained as a local lidocaine phenomenon (Figure 4).

Comparison of Lidocaine Levels in Patients After 1st and 2nd Liposuction (48h)

The second procedure was performed on 13 patients 48 hours after the operation (2016, 2017). 12 patients were treated with a tumescent solution with 1.0 mg / l epinephrine and one patient with 0.7 mg/l epinephrine in the infiltration solution (2018). In the lipedema center in the first surgery the lateral part of both legs is treated. In the second surgery the medial part of the legs is suctioned. This is mainly due to considerations of the lymphatic vessels. Before the start of the follow-up operation, an average lidocaine level of 0.26 $\mu\text{g/ml}$ was measured in the patients. The first peak of the lidocaine level after four hours

FIGURE 5. Comparison of lidocaine levels in patients after 1st and 2nd liposuction (48 hours). Comparison of the average lidocaine levels during the first and the subsequent operation: before and after the procedure, 4, 8, 12, 16, 20, 28, and 44 hours later. A significant increase in lidocaine levels during the second operation could only be found 8 hours after the procedure. In addition, it was found that after 28 hours the lidocaine levels of the patients during the second operation were significantly lower than during the first operation. Mean \pm SD. N=13. $P<0.05$.

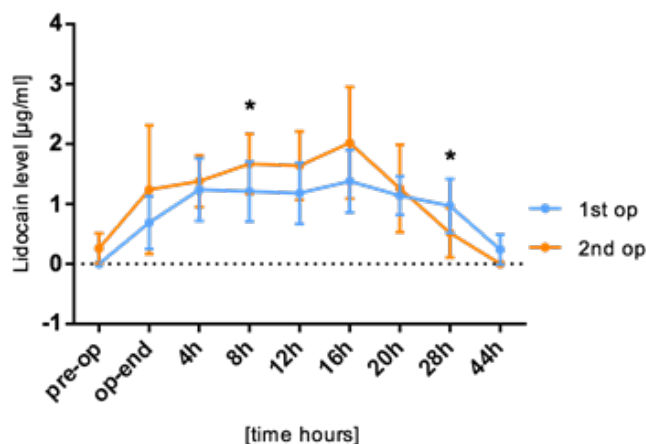


FIGURE 6. The maximum lidocaine level per patient. Horizontal line shows the cut-off at which the lidocaine levels were regarded as increased (3.0 µg/ml).

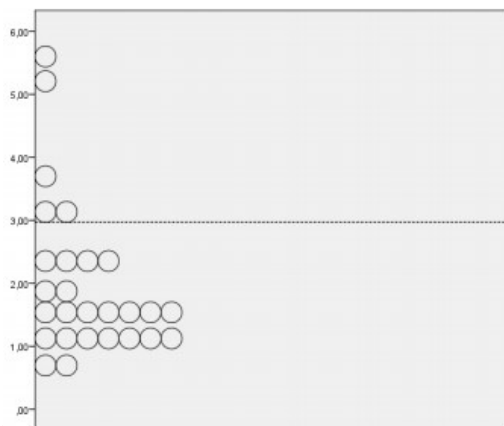


TABLE 4A.

Results of Pain (a) and Blood Loss (b) in the Postoperative Course.
Elevated subjective pain assessment in the postoperative course and how many patients received analgesics at each timepoint (post-operation, 4, 8, 12, 16, 20, 28, and 44 hours) (a). Comparison of hemoglobin and hematocrit before and after liposuction procedure and calculated drop in hemoglobin (b). N=27.

Time [h]	VAS		analgetic	
	Mean	σ	Yes	No
Post-op	4.44	2.46	--	--
4	3.70	1.94	4	19
8	3.12	1.60	13	10
12	2.20	1.31	8	13
16	2.05	1.17	6	16
20	1.77	1.15	0	20
28	2.02	1.85	2	19
44	2.46	1.82	2	9

TABLE 4B.

Time [h]	Pre-lipo		Post-lipo (44 hours)		Hemoglobin drop	
	Mean	σ	Mean	σ	Mean	σ
Hemoglobin	13.4	0.9	11.0	0.9	2.3	0.9
Hematocrit	39.7	2.9	32.9	2.7	6.7	2.8

cannot be observed during the follow-up operation. The average lidocaine level increased until it reached its maximum at 2.02 µg/ml after 16 hours. This was followed by a steep drop in lidocaine levels, so that after 28 hours they were below the comparable measurements of the first operation. Significant differences could be observed between 1st and 2nd liposuction using 1 mg epinephrine after 8 and 28 hours, where the latter was an even faster lidocaine excretion at the 2nd operation (Figure 5).

Influence of the Tumescient Solution on the Lidocaine Peak Level

To analyze which patients had an elevated level during treatment, the highest measured lidocaine concentration in the blood was analyzed for each patient. Lidocaine levels of at least 3.0 µg/ml were defined as increased. A total of five patients showed elevated levels. The average lidocaine peak level was 1.98 µg/ml ($\sigma = 1.24$) and occurred after 11.63 hours ($\sigma = 9.58$ h). If patients whose arms were treated were excluded from the analysis, the average peak level was 1.59 µg/ml ($\sigma = 0.67$), which can be found after 12.7 hours ($\sigma = 9.66$ h).

Outliers: The two peak values above 5 µg/ml were found in patients where a whole-arm type was aspirated, and venous blood was drawn from the back of the hand: This serum level shows a local artefact and does not represent the total serum level Figure 6.

Postoperative Pain and Blood Loss

The side effects were analyzed. All patients showed good or very good exercise capacity during the 44 hours analyzed. At the end of the operation, the patients reported an average pain sensation of 4.4 on the VAS scale. The postoperative sensation of pain decreases in the further course. For a large proportion of the patients, additional analgesic therapy is given in the course of postoperative care. To analyze the blood loss during the operation, the blood count before the operation and 44 hours after the operation was compared. On average, a decrease in hemoglobin by 2.3 g/dl and in hematocrit by 6.7% was observed.

Blood Pressure, Pulse, Respiratory Rate, SpO₂, Heart Enzymes

The blood pressure values remained stable over the entire investigation period. No increase in postoperative blood pressure was found. The average heart rate increased during the procedure and was significantly higher compared to the initial value at the end of the operation. ($P < 0.001$). The measurements after 4 and 8 hours were also significantly higher than before the operation. To test the statistical significance, a Wilcoxon test was carried out for connected samples. The average respiratory rate was significantly increased at 18.7 / min four hours after the procedure. In the further course the breathing frequency normalized. All patients appeared to be respiratory stable during treatment. No patient showed dyspnea or reduced oxygen saturation. An ANOVA with repeated measurements was carried out. There were no changes in oxygen saturation over time. None of the ECG examinations showed any abnormalities. The measured troponinT levels at the end of the operation and after 20 hours showed no increase in any patient (Data not shown). N=27.

Body Weight

The average body weight immediately after the operation is significantly higher at 95.7kg than before the operation ($P < 0.001$). The body weight decreases continuously over the next 44 hours and after 44 hours the body weight is still 1.92 kg

above the starting point.

Eyelid Edema

Minor eyelid edema was found in two patients after 20 hours. The next time the patient was examined, the eyelid edema was no longer visible after 28 hours.

Drinking Amount

The patients drank 2.9 liters of water within the first 20 hours postoperatively. In the following 24 hours it was only 2.38 liters. This results in a total liquid supply of 5.35 liters.

Diameter Vena Cava Inferior

The diameter of the inferior vena cava was measured in the course of the ultrasound examinations. No difference was found in the filling state and diameter of the vena cava inferior.

Side Effects

Overall, mild side effects of the treatment were recorded in the postoperative visits in 12 out of 27 patients. Nine patients said they had a short episode with poor circulation. Five patients showed up with a reddened and overheated skin color in the course of a mild SIRS during the visit.

DISCUSSION

Although the amount of lidocaine administered with tumescent anesthesia is many times higher than the maximum dose recommended under local anesthesia, tumescent anesthesia has proven to be a very safe anesthetic procedure.^{29,30} A major factor in the slow absorption of lidocaine is reduced blood flow in the operating area.³¹ Another factor that is important for the absorption of lidocaine is the lipophilicity of the substance. Adipose tissue has a very high binding capacity for lidocaine and only releases the bound active ingredient slowly. One gram of fat can bind up to one milligram of lidocaine.³² Several authors suspect that the high lidocaine binding capacity of the adipose tissue is largely responsible for the slow absorption of the lidocaine in the vascular system. If there is no firmness with TLA solution (watermelon consistence or state of tumescence) we have to assume a situation of intramuscular and subcutaneous injection with a high end of 7 mg/kg lidocaine.³³ In contrast to conventional local anesthesia, the drugs are used very diluted in tumescent anesthesia. While high peak levels can be observed quickly after intravenous or intramuscular administration of lidocaine, the absorption of lidocaine after subcutaneous administration is slow at a constant rate and regardless of the amount of lidocaine remaining in the adipose tissue.³⁴ Klein compares the pharmacokinetics of lidocaine in tumescent anesthesia with the slow absorption of a substance from a depot injection or a drug with a sustained release effect or a continuous 12–16 hour intravenous infusion.²⁵ Previously published data on the pharmacology of tumescent anesthesia come mainly from studies with small amounts of tumescent solution administered, high lidocaine concentration of the tumescent solution of 500–

1500 mg/l and small liposuction with aspirate amounts of less than three liters. With 11.4 l, the amount of tumescent solution applied in this study is higher than in comparative studies. This can be explained by the full tumescent technique, in which tumescent liquid is introduced until the tissue has a firm turgor. Due to the laxity of the skin, patients with lipedema, especially after weight loss, need significantly more fluid until the tissue is full, this happens mostly in lipedema patients after bariatric surgery. However, infiltration of high levels of tumescent fluid with dissolved lidocaine could increase the risk of lidocaine-associated toxicity. To reduce this risk, we reduced the lidocaine concentration of the tumescent solution to 233 mg/l in this study and since 2016 routinely. In the event of pain during suction, a solution with 400 mg/l was added for the subsequent infiltration. The use of a TLA with 0.0233 lidocaine enables a larger volume liposuction, especially since a toxic lidocaine level is reached much later than with the originally 0.04 concentration. The recommendations regarding a safe amount of lidocaine to be administered vary widely. By Ostad et al a total of up to 76 mg lidocaine per kg body weight was administered without any signs of toxicity.³⁵ Many authors consider a lidocaine dose of up to 55 mg/kg body weight to be safe, while other investigators consider this amount to be risky and recommend lower limit values^{13,36} In a recent pharmacological study by Klein et al, lidocaine plasma levels were examined at different lidocaine doses. As a result, he finds that a lidocaine amount of 55 mg/kg body weight is probably safe in most cases, but a maximum dosage of 45 mg/kg body weight is recommended due to the low safety reserve.²⁵ With an infiltration of 34.23 mg / kg body weight lidocaine, the present study showed a maximum lidocaine concentration in plasma with an average of 1.58 µg / ml, which was measured after an average of 11.8 hours. Klein was able to observe average lidocaine levels after 12 to 14 hours using tumescent anesthesia with a lidocaine concentration of 1000 mg/l and a dosage of 34 mg/kg body weight.²⁰ In a similar study involving twelve patients, peak lidocaine levels between 0.6 and 3.6 µg/ml were measured six to twelve hours after the end of the infiltration.³⁷ In both studies, however, only small amounts of tumescent solution were applied. The lidocaine concentration in the tumescent solution and the chosen anesthesia procedure could also be influencing factors on the absorption of lidocaine. There is evidence that a low-concentration lidocaine solution causes delayed absorption of the lidocaine. Burk et al, who used a similarly low lidocaine concentration in the tumescent solution (250 mg/l) in the course of several interventions, found the maximum peak plasma levels of lidocaine after 12 hours with 21 mg/kg body weight in an administered lidocaine dose between 0.6 and 1.6 µg/ml.³⁸ Kenkel et al also administered a lidocaine dose of 21 mg/kg body weight with a lidocaine concentration of 300 mg/l. They found 88 average peak values of 1.8 µg/ml, which were measured after 12.8 hours.³⁹ Despite a significantly higher lidocaine dose of 34 mg/kg, the mean maximum lidocaine concentration of 1.58 µg/ml is lower in this study than in Kenkel et al In the previously

mentioned studies, the intervention in general anesthesia and "superwet" technique is carried out with the infiltration of small amounts of liquid. Kenkel with 4.7 liters uses significantly less tumescent fluid than in this study (11.4 liters). Klein describes that the absorption of lidocaine is additionally reduced in the tumescence technique because the high tissue pressure further reduces the blood circulation and the diffusion of the lidocaine into the vascular system is made more difficult due to the high fluid content.²⁷ Therefore, although the average lidocaine concentrations measured in both comparative studies are well below the pre-toxic limit of 3 µg/ml, the use of the tumescence technique may increase safety. Although the administration of low-concentration tumescent solutions should delay the absorption of lidocaine into the vascular system, the maximum lidocaine levels are found very early in 35% of our patients. In 8 out of 27 patients the lidocaine peak levels cannot be measured after 8 to 16 hours, as is typical for tumescent anesthesia, but within the first four hours. After the rapid rise within the first four hours, this study shows almost a plateau until the levels begin to fall again after 16 hours. Oba et al found a maximum plasma level after only three hours when examining five patients using a tumescent solution with 250 mg / l lidocaine and a lidocaine dose of 28 mg / kg body weight.³⁹ The results of this study confirm the safety of tumescent anesthesia in patients with lipedema. By using a tumescent solution of 233 mg lidocaine per liter, despite the administration of 11.4 liters of tumescent liquid, the safe total dose of 35 mg / kg lidocaine is not exceeded. Although the total amount of epinephrine supplied was significantly reduced by using a tumescent solution with 0.7 mg epinephrine per liter, the measured epinephrine levels in the blood showed no significant differences from a comparison group with a tumescent solution with 1 mg epinephrine per liter. The infiltration of large amounts of tumescent fluid is well tolerated hemodynamically without signs of hypervolemia. Postoperatively, the patients have good physical exercise capacity at all times. We not only analyzed the serum levels per kg body weight, but also per kg total fat. This course is relatively parallel in the rather heavier patients. However, slim patients with lipedema with a total fat of approx. 10 kg, one has to be careful not to remove too much fat, especially since the storage capacity of the lidocaine is lost to the fat and the patients can develop circulatory problems and toxicity. In patients with a BMI over 30, 15–20% of the total fat can be removed in one session. With lipedema where approximately 1.5–2 liters of tumescent solution per liter fat extracted can be infiltrated.¹³

CONCLUSION

Based on our study and the results obtained, we primarily used the measurement of the total fat content to evaluate the lidocaine dose, but also the amount of fat to be removed. We concluded that the amount of lidocaine per kg of fat and not just per kg of body weight has to be calculated. In addition, liposuction should not be performed with more than 15-20%

of the total fat. This particularly affects slim lipedema patients with a total fat of less than 12kg. The expected hypovolemia must be compensated by oral fluid administration, whereby approx. 50-100% of the removed fat must be substituted by fluid. The administration of a 0.0233% lidocaine dose is sufficient for anesthesia, but the requirement is that the subcutaneous fat tissue has a watermelon-like consistency - full tumescence.¹³ The use of sedoanalgesia with short-acting drugs (midazolam, propofol, remifentanyl) administered by a specialist in anesthesia and intensive care medicine during the procedure, also makes things easier for the patient. Follow-up care and patient clearance should be carried out by the same specialist. Between the individual procedures, there should be a break of at least 4 weeks. The arms should be performed in a separate procedure, especially since the increased resorption in the axillary area cannot be excluded. For patients over the age of 60, the pharmacological limits should be reduced by 30%. By the end of our study (January 2018) we had treated 580 patients with lipedema in an average of 3 sessions. Based on our results and the measures that followed, we have seen no more complications or postoperative inpatient stays in around 400 patients over the past 3 years.

In this study it was shown for the first time that if the general guidelines for liposuction are adhered to, large interventions can also be carried out safely in ambulatory lipedema patients. This study thus contributes to strengthening the evidence on the safety of liposuction in tumescent anesthesia in lipedema patients.

DISCLOSURES

We exclude any conflict of interest and guarantee that all authors are in complete agreement with the contents and submission of this manuscript. Furthermore, we declare that our work is original research, unpublished, and not submitted to another journal.

REFERENCES

- Rudkin GH, Miller TA. Lipedema: a clinical entity distinct from lymphedema. *J Plast Reconstr Aesthet Surg.* 1994;94:841-849.
- Sattler G, HE Rapprich S, Mössler K, Hagedorn M. Neue operative Behandlungsmöglichkeiten bei benignen Fettgewebskrankungen. *Z Hautkr.* 1997;72:4.
- Cornely ME. Lymphologische Liposkulptur. *Der Hautarzt.* 2007;58:6.
- Habbema, L. Safety of liposuction using exclusively tumescent local anesthesia in 3,240 consecutive cases. 2009;35:1728-1735.
- Hanke CWB, G. Block S. Safety of liposuction in 15,336 patients. National survey results. *Dermatol Surg.* 1995;21:4.
- Rapprich S, Dingler A, Podda M. Liposuction is an effective treatment for lipedema-results of a study with 25 patients. *J Dtsch Dermatol Ges.* 2011;9:33-40.
- Reich-Schupke S, Schmeller W, Brauer WJ, et al. S1 guidelines: Lipedema. *J Dtsch Dermatol Ges.* 2017;15:758-767.
- Sandhofer M, SP, Anderhuber F. Lipödem. *J Ästhetische Chirurgie.* 2017;10:10.
- Schmeller W, Meier-Vollrath, I. (2006). Tumescent liposuction: a new and successful therapy for lipedema. *J Cutan Med Surg.* 2006;10:7-10.
- Dadras M, Mallinger PJ, Corterier CC, Theodosiadi S, Ghods M. liposuction in the treatment of lipedema: a longitudinal study. *Arch Plast Surg.* 2017;44:324-331.
- Baumgartner A, Hueppe M, Schmeller W. (2016). Long-term benefit of liposuction in patients with lipoedema: a follow-up study after an average of

AQ: References were edited to conform to JDD style. Check references throughout text and confirm if accurate.

- 4 and 8 years. *Br J Dermatol.* 2016;174:1061-1067.
12. Fetzer A. Specialist approaches to managing lipoedema. *Br J Community Nurs.* 2016;S30-35.
 13. Sandhofer M, Hanke CW, Habbema L, et al. Prevention of progression of lipedema with liposuction using tumescent local anesthesia: results of an International Consensus Conference. *Dermatol Surg.* 2020;46:220-228.
 14. Child AH, Gordon KD, Sharpe P, et al. (2010). Lipedema: an inherited condition. *Am J Med Genet A.* 2010;152A:970-976.
 15. Romeijn JRM, de Rooij MJM, Janssen, Martens, H. Exploration of patient characteristics and quality of life in patients with lipoedema using a survey. *Dermatol Ther.* 2018;8:303-311.
 16. Bilancini S, Lucchi M, Tucci S, Eleuteri P. Functional lymphatic alterations in patients suffering from lipedema. *Angiology.* 1995;46:333-339.
 17. Dudek JE, Bialaszek W, Ostaszewski P. (2016). Quality of life in women with lipoedema: a contextual behavioral approach. *Qual Life Res.* 2016;25:401-408.
 18. Forner-Cordero I, Szolnoky G, Forner-Cordero A, and Kemeny L. (2012). Lipedema: an overview of its clinical manifestations, diagnosis and treatment of the disproportional fatty deposition syndrome - systematic review. *Clin Obes.* 2012;2:86-95.
 19. Lohrmann C, Foeldi E, Langer M. (2009). MR imaging of the lymphatic system in patients with lipedema and lipo-lymphedema. *Microvasc Res.* 2019;77:335-339.
 20. Klein JA. (1990a). Tumescent technique for regional anesthesia permits lidocaine doses of 35 mg/kg for liposuction. *J Dermatol Surg.* 1990;16:248-263.
 21. Klein JA. The tumescent technique. Anesthesia and modified liposuction technique. *Dermatol Clin.* 1990;8:425-437.
 22. Samdal F, Amland PF, Bugge JF. Blood loss during liposuction using the tumescent technique. *Aesthetic Plast Surg.* 1994;18:157-160.
 23. Priglinger E, Strohmeier K, Weigl M, et al. SVF-derived extracellular vesicles carry characteristic miRNAs in lipedema. *Sci Rep.* 2020;10:7211.
 24. Priglinger E, Wurzer C, Steffenhagen C, et al. (2017). The adipose tissue-derived stromal vascular fraction cells from lipedema patients: Are they different? *Cytotherapy.* 2017;19:849-860.
 25. Klein JA, Jeske DR. Estimated Maximal Safe Dosages of Tumescent Lidocaine. *Anesth Analg.* 2016;122:1350-1359.
 26. Ghods M, Kruppa P. Surgical treatment of lipoedema. *J Ästhetische Chirurgie.* 2018;50:400-411.
 27. Klein JA. (1999). Anesthetic formulation of tumescent solutions. *Dermatol Clin.* 1999;17:751-759, v-vi.
 28. Marshall MS-S C. (2011). Prävalenz des Lipödems bei berufstätigen Frauen in Deutschland: (Lipödem-3-Studie). *Phlebologie.* 2011;40:8.
 29. Rubin JP, Bierman C, Rosow CE, et al (1999). The tumescent technique: the effect of high tissue pressure and dilute epinephrine on absorption of lidocaine. *Plast Reconstr Surg.* 1999;103:990-996; discussion 997-1002.
 30. Thomasy M, Pypendop BH, Ilkiw JE, Stanley SD. Pharmacokinetics of lidocaine and its active metabolite, monoethylglycinexylidide, after intravenous administration of lidocaine to awake and isoflurane-anesthetized cats. *Am J Anim Vet Sci.* 2005;66, 1162-1166.
 31. Luby M, Rohrich RJ, Brown SA. (2004). Pharmacokinetics and safety of lidocaine and monoethylglycinexylidide in liposuction: a microdialysis study. *Plast Reconstr Surg.* 2004; 114, 516-524; discussion 525-516.
 32. de Jong RH. Mega-dose lidocaine dangers seen in "tumescent" liposuction. *J Clin Monit Comput.* 2000;16:77-79.
 33. Miller A, Mandeville J. Predicting and measuring fluid responsiveness with echocardiography. *Echo Res Pract.* 2016;3:G1-G12.
 34. Conroy PH, O'Rourke J. Tumescent anaesthesia. *Surg-J R Coll Surg E* 2013;11: 210-221.
 35. Ostad A, Kageyama N, Moy RL. Tumescent anesthesia with a lidocaine dose of 55 mg/kg is safe for liposuction. *Dermatol Surg.* 1996;22: 921-927.
 36. Haeck PC, Swanson JA, Gutowski KA, Basu CB, Wandel AG, Damitz LA, Reisman NR, Baker SB, Committee APS. (2009). Evidence-based patient safety advisory: liposuction. *Plas Reconstr Surg.* 2009;124:28S-44S.
 37. Samdal F, Amland P, Bugge JF. Plasma lidocaine levels during suction-assisted lipectomy using large doses of dilute lidocaine with epinephrine. *Plas Reconstr Surg.* 1994;93:1217-1223.
 38. Burk RW 3rd, Guzman-Stein G, Vasconez LO. Lidocaine and epinephrine levels in tumescent technique liposuction. *Plast Reconstr Surg.* 1996;97:1379-1384.
 39. Kenkel JM, Lipschitz AH, Shepherd G, Armstrong VW, Streit F, Oellerich, Oba H. (2003). Large-volume tumescent anesthesia for extensive liposuction in oriental patients: lidocaine toxicity and its safe dose level. *Plast Reconstr Surg.* 2003;111:945-946.

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