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Effect of adrenaline concentration in tumescence solution on intraoperative hemodynamics of liposuction patients: A randomized triple-blind trial

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ABSTRACT

Background: Epinephrine in liposuction solution mediated vasoconstriction thus decrease in adrenergic side effects, local anesthetic toxicity, and bleeding. The optimum safe adrenaline concentration was not well investigated.

Aim: This study aimed to compare between adrenaline 1 mg/L and 2 mg/L in tumescent fluid concerning hemodynamics during abdominal liposuction operations.

Methods: Forty cases scheduled for liposuction for abdomen and flanks and body were involved in this randomized, triple-blind, controlled trial. Cases were randomized equally into two groups. Group A (low adrenaline concentration group): received 1 mg per liter of epinephrine. Group B (high adrenaline concentration group): received 2 mg per liter of epinephrine.

Results: Intraoperative heart rate and mean arterial blood pressure at base line were insignificantly different between both groups (p value > 0.05) while at 30, 60, 90, and end of surgery were significantly higher in group B group as opposed to group A (p value < 0.05). Incidence of sinus tachycardia and PVCs were significantly higher in group B than group A ($P < 0.05$), while surgeon satisfaction was comparable between both groups (p value > 0.05).

Conclusions: In liposuction procedures, the safest adrenaline concentration is 1 mg/L as evidenced by hemodynamics stability and surgeon satisfaction thus even in high volume liposuction, the adrenaline concentration should not exceed 1 mg/L and should be handled to cover the used crystalloid solution.

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1. Introduction

Weight gain over time, is associated with transformation of mesenchymal stem cells into fat cells, leading to a rise in the number of fat cells in addition to an increase in fat cell size during the first weight gain [1]. Exercise and diet have been demonstrated to reduce the size of fat cells, but not their quantity, which is known as "resistant fat." [2].

Liposuction operation is one of the most common cosmetic surgeries in the recent years. It is simply the process of removal of excess unwanted fat from some areas of the body, consequently lowering the number of fat cells and the amount of resistant fat [3]. The most common sites requested for liposuction are the abdomen, flanks, arms, thighs, and back in females, while liposuction in males is mainly from the buttocks and breasts [4]. Various liposuction procedures have been established including manual liposuction, suction assisted lipectomy (SAL), ultrasound assisted liposuction (UAL-VASER), power assisted liposuction (PAL-MICROAIRE) and laser liposuction (COOL LIPO) [5].

Tumescent liposuction refers to the administration of large amounts of diluted local anaesthetic and epinephrine to enhance anaesthesia and reduce blood loss. Concerns exist regarding the optimal dose of local anaesthetic, the use of general anaesthesia in liposuction, and the situation in which the selected liposuction technique is utilized [6].

Although the safe maximum dosage of lignocaine is 6 mg/kg, Klein reported that in tumescent anaesthesia, significantly greater dosages, up to 45–55 mg/kg body weight, can be provided safely [7,8]. This is due to the fact that during tumescent anaesthesia, the absorption rate of lignocaine is slow, resulting in lower peak concentrations and, consequently, reduced toxicity [9].

Like certain other buffered anaesthetic solutions, sodium bicarbonate can be mixed with lidocaine at a ratio of 1 mEq per 10 mL. The pH of this solution is physiological. Nonetheless, consideration should also be paid to lidocaine's pKa, which is 7.9. To obtain this concentration, even more bicarbonate (20 mEq/L) must be introduced to the tumescent mixture. To

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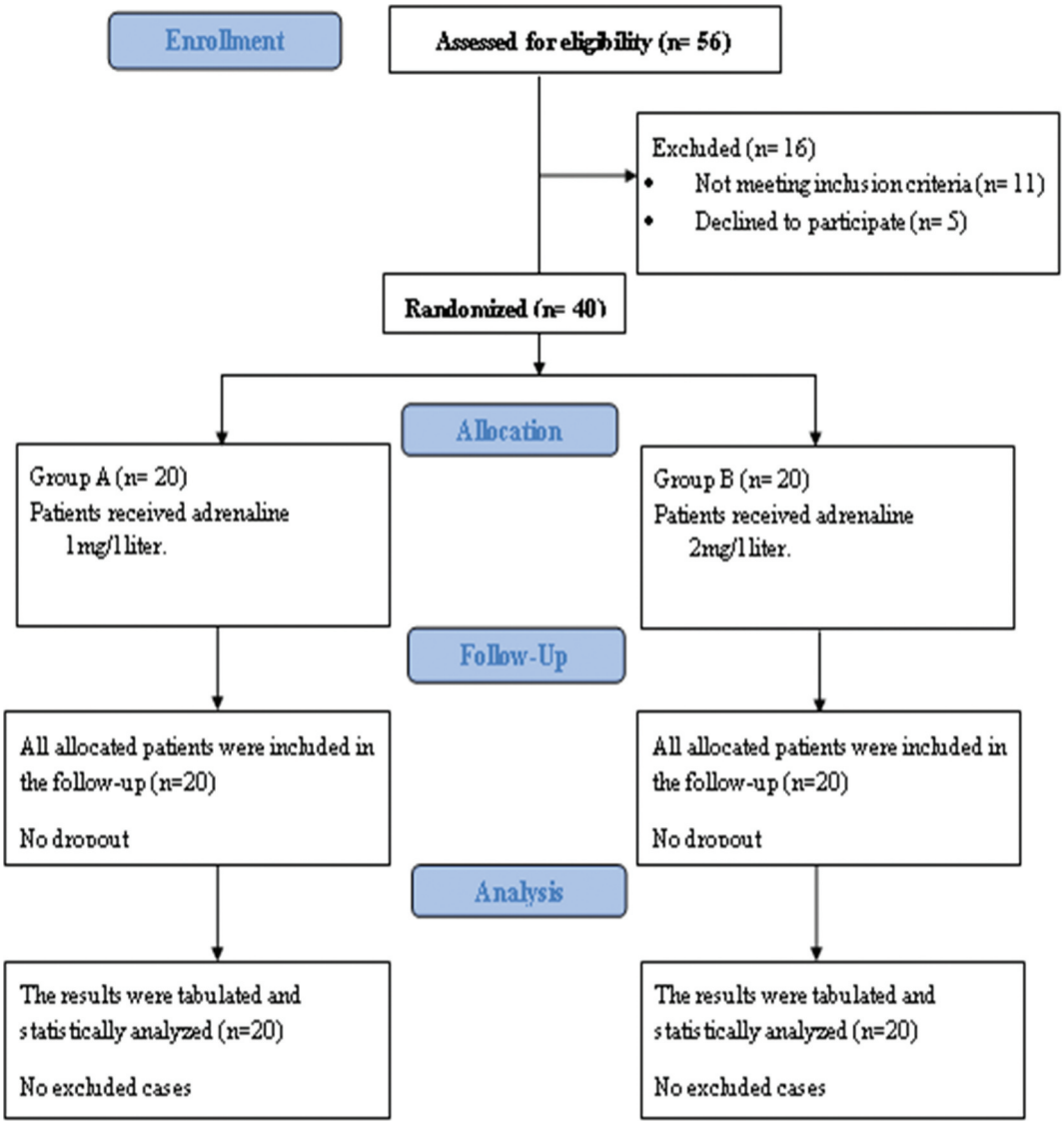

Figure 1. CONSORT flowchart of the enrolled patients.

obtain this concentration, even more bicarbonate (20 mEq/L) must be introduced to the tumescent mixture [10].

Slow absorption of lignocaine is assisted by diluted adrenaline in saline ensuring vasoconstriction, so reducing systemic absorption and hemorrhage [6]. The recommended concentration of adrenaline in the tumescent solution is 0.5-2 mg/L with maximum dose 5 mg (2.5 L) based on the vascularity of the tissue. The concentration is 2 mg/L in the more vascular tissues and 0.5 mg/L in the less vascular parts of the body. The dose should not go above 50 µg/kg. If it is expected that the maximum dose will be exceeded, the procedure should be performed in multiple steps [11].

The optimum safe adrenaline concentration was not well studied, thus herin this study aimed to compare between adrenaline 1 mg/L and 2 mg/L in tumescent fluid concerning hemodynamics during abdominal liposuction operations.

2. Materials and methods

This prospective randomized triple blinded trial involved 40 cases of age greater than 21 years old, both sexes, American Society of Anesthesiologists (ASA) physical status classification I who underwent liposuction for abdomen, flanks, and body. The study was done from April 2023 to June 2023. The study was carried out at Benha university Hospitals.

Each patient provided written informed consent. The research was performed after the approval of the Ethical Committee Benha university Hospitals (approval code: RC.3.1.2023), registration of clinicaltrials.gov (ID: NCT05822765) and the date of first registration was (21/04/2023).

Exclusion criteria were bleeding disorders, anemia or hemoglobin level less than 11 g/dl, cardiovascular diseases, uncontrolled diabetes mellitus, collagen disorders, and pregnancy.

3. Randomization and blindness

Computer-generated randomization numbers were applied to randomly allocate 40 cases equally into two groups. Group A (low adrenaline concentration group): received 1 mg per liter of epinephrine. Group B (high adrenaline concentration group): received 2 mg per liter of epinephrine. Sealed envelopes were used to ensure random allocation by a nurse who did not take apart in the study. Cases, observers, and outcome assessors were blinded to the experimental medication. Drugs were prepared by an additional pharmacist who did not join in the remaining phases of trial. All containers were identical in appearance.

4. Preoperative

Photos were taken prior to alongside information about each patient's body mass index, percentage body fat, height, and weight. History taking, clinical evaluation, and routine laboratory investigations were done and spread according to the cases. Marking of the patients was done to localize areas of treatment. Insertion of an intravenous line and a urine catheter. Cases were connected to a monitor consisted of pulse oximetry, non-invasive blood pressure, 5-lead ECG, a temperature probe, and capnography.

5. Intraoperative

The cases were subsequently transferred to the operating room to undergo surgery. 8 ~ 10 mL/kg of Ringer's solution was infused. No extra sedatives were given as a premedication.

To induce GA, 2 mg/kg IV propofol and 1 µg/kg IV fentanyl were administered. Rocuronium 0.9 mg/kg IV was administered to assist endotracheal intubation. Anesthesia maintenance was carried out with 1–1.5% isoflurane in 50% oxygen. Increasing dosages of 0.03 mg/kg cis-atracurium were administered intravenously when needed, and up doses of fentanyl were given as needed.

Mechanical ventilation parameters were adapted to keep $EtCO_2$ at 30–35 mmHg. Additional doses of 1 µg/kg fentanyl were provided intravenously whenever the MAP or heart rate (HR) increased by more than 20% from initial values. The consumption of intraoperative fentanyl (including induction dosage) and isoflurane was documented.

Multiport blunt cannulas (2.4–4.0 mm openings) were used for liposuction. Aspirated tumescent fluid, fat, and tissue debris were collected in a bottle of the suction machine under negative pressure. All surgeries were performed under GA in combination with tumescent local anesthesia (500 mg lidocaine, 1 mg or 2 mg epinephrine, 10 ml 8.4% sodium bicarbonate, 1000 ml 1 normal saline), using the super wet technique (1:1 ratio of the tumescent fluid infiltration: lipoaspiration). Patients were randomly divided into 2 groups 20 patient each.

Group A: Tumescence fluid contained Epinephrine concentration of 1:1000000 (one ampoule 1 mg per liter) lidocaine 500 mg and sodium bicarbonate 8.4% 10 ml per liter, while Group B: Tumescence fluid contained Epinephrine concentration of 1:500000 two ampoule 2 mg/liter with same lidocaine and bicarbonate dose. Noninvasive BP and HR were recorded every 10 minutes and results were recorded. Urinary output and fluid replacement were also recorded.

The safe maximum dose of lidocaine is 35 mg/kg. The maximum volume of suctioned fluid did not exceed 4000 ml in any patient. Infected areas were fitted with temporary drains that were removed within one to two days. Compression garments were worn for two to three weeks.

The same surgeon conducted all surgeries. Surgeon' satisfaction was measured immediately postoperative using a five-point Likert scale consisting of "very dissatisfied," "dissatisfied," "unsure," "satisfied," and "highly satisfied.

The neuromuscular blockade was restored by 0.05 mg/kg neostigmine and 0.02 mg/kg atropine. Cases were given IV paracetamol 1 gm/8 hours. If VAS > 3 was observed, rescue analgesia (pethidine 50 mg IV) was administered.

Incidence of sinus tachycardia and PVCs were recorded.

The primary outcome was HR. The secondary outcome was MAP, at different time intervals.

6. Sample size calculation

The sample size determination was done by G*Power 3.1.9.2 (Universitat Kiel, Germany). We performed a pilot study due to absence of previous similar studies (5 cases in each group) and we found the mean difference (±SD) of heart rate at 30 minutes was 2.4 ± 1.87 between group A and group B. The sample size was calculated based on the following considerations: 1.28 effect size, 95% confidence limit, 95% power of the study, group ratio 1:1 to be >17 patients in each group. To overcome dropouts, 3 patients were added in each group; therefore, we recruited 20 cases in each group.

7. Statistical analysis

SPSS v28 (IBM©, Armonk, NY, USA) was used for statistical analysis. By the Shapiro–Wilks test and histograms, the data normality distribution was tested. As mean and standard deviation (SD), quantitative parametric data were expressed and were analyzed by unpaired student t-test. Qualitative variables were presented as frequency and percentage (%) and analysed

Table 1. Demographic data, and duration of surgery of the studied groups.

		Group A ($n = 20$)	Group B ($n = 20$)	P value	Mean difference (95%CI) Or RR (95%CI)
Age (years)		27.2 ± 9.24	30.2 ± 10.65	0.347	−3(−9.38: 3.38)
Sex	Male	9 (45%)	7 (35%)	0.519	1.29(0.6:2.77)
	Female	11 (55%)	13 (65%)		
Weight (kg)		80 ± 10.84	81.4 ± 10.3	0.678	−1.4(−8.17: 5.37)
Height (m)		1.68 ± 0.06	1.69 ± 0.07	0.558	−0.01(−0.06: 0.03)
BMI (kg/m^2)		28.46 ± 4.08	28.64 ± 4.39	0.897	−0.18(−2.89: 2.54)
Duration of surgery (min)		152.75 ± 10.19	148.5 ± 11.13	0.216	4.25(−2.58: 11.08)

Data are presented as mean ± SD or frequency (%), BMI: body mass index, RR: relative risk.

Table 2. Intraoperative heart rate of the studied groups.

	Group A	Group B	P value	Mean difference (95%CI)
Base line	73.5 ± 4.39	72.55 ± 4.73	0.514	0.95(−1.97: 3.87)
30 min	86.35 ± 6.35	98.65 ± 2.98	0.000*	−12.3(−15.48: −9.12)
60 min	80.45 ± 4.94	94.5 ± 4.25	0.000*	−14.05(−17: −11.1)
90 min	82.95 ± 9.16	96.4 ± 6.44	0.000*	−13.45(−18.52: −8.38)
End of surgery	87.05 ± 6.81	91.85 ± 7.11	0.035*	−4.8(−9.26: −0.34)

Data are presented as mean ± SD, *: Significant when P value ≤ 0.05.

by Chi-square or Fisher's exact test when applicable. A two-tailed P value <0.05 was judged statistically significant.

8. Results

In this trial, 56 cases were evaluated for eligibility, 11 cases did not match the criteria and 5 cases refused to join in the trial. The residual 40 cases were allocated randomly into two groups in a parallel manner and allocation ratio 1:1 (20 cases in each). All allocated cases were monitored and analyzed statistically. (Error! Reference source not found.) Figure 1.

Age, sex, weight, Height, BMI, and duration of surgery were matched between the two studied groups (Table 1).

Intraoperative heart rate at base line was insignificantly different between both groups (p value > 0.05) while at 30, 60, 90, and end of surgery was significantly higher in group B group as opposed to group A (p value < 0.05) (Table 2).

Intraoperative mean arterial blood pressure (MAP) at base line was insignificantly different between both groups (p value > 0.05) while at 30, 60, 90, and end of surgery was significantly higher in group B group as opposed to group A (p value < 0.05) (Table 3).

Incidence of sinus tachycardia and PVCs were significantly higher in group B than group A (P < 0.05), while surgeon satisfaction was comparable between both groups (p value > 0.05) (Table 4).

9. Discussion

In the tumescence procedure, very large quantities of diluted local anaesthetic are injected into the subcutaneous tissue combined with additions of adrenaline and sodium bicarbonate for tissues expansion and to make them hard, puffy, and turgid, i.e., the final objective of

Table 3. Intraoperative MAP of the studied groups.

	Group A	Group B	P value	Mean difference (95%CI)
Base line	91.4 ± 5.51	92.95 ± 5.11	0.362	−1.55(−4.95: 1.85)
30 min	104.7 ± 7.97	113.9 ± 6.75	0.000*	−27.55(−32.28: −22.82)
60 min	96.3 ± 5.6	100.5 ± 3.36	0.007*	−4.2(−7.16: −1.24)
90 min	101.1 ± 5.01	114.85 ± 7.98	0.000*	4.7(0.44: 8.96)
End of surgery	94.15 ± 6.75	107.9 ± 11.92	0.000*	−13.75(−19.95: −7.55)

Data are presented as mean ± SD, *: Significant when P value ≤ 0.05.

Table 4. Incidence of sinus tachycardia, PVCs, and surgeon satisfaction in the studied groups.

		Group A ($n = 20$)	Group B ($n = 20$)	P value	RR (95%CI)
Sinus tachycardia		1 (5%)	9 (45%)	0.008*	0.16(0.02:1.03)
PVCs		1 (5%)	8 (40%)	0.019*	0.18(0.028: 1.18)
Surgeon satisfaction	Satisfied	12 (60%)	9 (45%)	0.342	1.33(0.73:2.44)
	Highly satisfied	8 (40%)	11 (55%)		

Data are presented as mean ± SD, *: Significant when P value ≤ 0.05, PVCs: Premature ventricular contractions.

strong tissue turgor. This produces a surface from which suctioning fat is easy and blood loss is reduced [11].

Depending on the aspirated volume, liposuction can be either high volume (>4,000 mL aspirated) or low volume (4,000 mL aspirated) [12].

Lignocaine is the most frequently used local anaesthetic in tumescent solutions, with a maximum dose of 7 mg/kg when combined with adrenaline. The suggested maximum dose of lignocaine for the majority of patients is 55 mg/kg, with a range of 35–55 mg/kg for liposuction patients [6]. Pharmacokinetic studies revealed that peak concentrations of lignocaine and its active metabolite monoethylglycinexylidide are reached eight to thirty-two hours after first infiltration [13]. Dose, systemic absorption rate, and elimination are the most important factors that are responsible for lignocaine toxicity. To allow larger dose of lignocaine in liposuction solution, vasoconstrictors as adrenaline is added to decrease systemic absorption of lignocaine and decrease bleeding [6].

Due to its vasoconstrictive impact, epinephrine 1:1000 [1 mg/mL] is typically added to the wetting solution. This results in less blood in the aspirate and a longer duration of local anaesthetic effect [14]. Also, epinephrine mediated vasoconstriction prevents more absorption of that drug resulting in decline in adrenergic adverse events and local anesthetic toxicity [15]. However, to enhance surgical outcomes, the volume of wetting solution has been raised, and it was reported to exceed 5–10 mg in large volume cases [16]. Therefore, the safety of high adrenaline concentration is crucial to be investigated.

Our results demonstrated that higher concentrations (2 mg/L) were associated with hemodynamic instability and higher incidence of sinus tachycardia and PVCs while surgeon satisfaction was comparable between both groups.

It was linked between myocardial infarction [MI], cardiac arrhythmias, fatal asystole, pulmonary overload, and pulmonary edema during liposuction surgeries with adrenaline in liposuction solution [17].

Rubin et al. [18] found that epinephrine (1:1,000,000) delays the lidocaine absorption delivered by the tumescent method. The addition of 1:1,000,000 epinephrine considerably delayed the time to peak plasma concentration by more than seven hours. Adrenaline concentration in the tumescent fluid significantly affected hemodynamics intraoperatively. 1:1000000 concentration of adrenaline is safer with less increase in heart rate and blood pressure. Prasetyono et al. [19] found that in hand and upper extremity surgery, one-per-milliliter tumescent solution generated a clean surgical field. It proved safe and effective for a wide range of indications which confirm our findings regarding surgeon satisfaction as adrenaline act as adrenoreceptor agonist resulted in vasoconstriction that decrease bleeding tendency.

Lidocaine and epinephrine dosage safety was examined by Burk et al. [20]. In 10 patients having liposuction using the tumescent method alone, all patients exhibited safe lidocaine concentrations at all intervals, with the greatest levels occurring in patients who received intravenous lidocaine upon the induction of anaesthesia. The peak epinephrine readings occurred at the 3-hour blood draw and were around four times the normal range. There was no subjective or objective evidence of lidocaine or epinephrine toxicity in any patient.

However, in contrast to our findings, Sonbol et al. [16] reported higher incidence sinus tachycardia and hemodynamics instability in patients received adrenaline 1 mg/L in their liposuction solution, but this difference from our findings could be justified as they compared this solution with Mg which attenuated adverse events of adrenaline.

Other contributing factors in hemodynamic changes are type and rate of liposuction, one or two suction machines used, the amount of tumescent fluid, the surface area of liposuction, squeezing and in which part of the body is the suction done.

Limitations: The trial was in a single center with a relatively short follow-up period. Thus, further large-scale multicenter collaboration studies and longer monitoring duration are necessary to validate our findings.

10. Conclusions

In conclusion: in liposuction procedures, the safe epinephrine concentration is 1 mg/L as evidenced by hemodynamics stability and surgeon satisfaction thus even in high volume liposuction, the epinephrine concentration should not exceed 1 mg/L and should be handled to cover the used crystalloid solution.

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Author contributions

All authors participated in preparing this clinical trial and approved of the work as it is being submitted. All authors read and approved the final manuscript.

Availability of data and materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Each patient provided written informed consent. The research was performed after the approval of the Ethical Committee Benha university Hospitals (approval code: RC.3.1.2023), registration of clinicaltrials.gov (ID: NCT05822765) and the date of first registration was (21/04/2023).

Disclosure statement

No potential conflict of interest was reported by the author(s).

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