Aesth Plast Surg (2020) 44:820–829
https://doi.org/10.1007/s00266-019-01573-5

ORIGINAL ARTICLE BODY CONTOURING

Randomized Trial of Deep Vein Thrombosis Chemoprophylaxis with Bemiparin and Enoxaparin in Patients with Moderate to High Thrombogenic Risk Undergoing Plastic and Reconstructive Surgery Procedures

Francisco Revilla-Peñaloza[1,4] · Paul Jay Olsoff-Pagovich[2] · Jose Ramon Ochoa-Gomez[2] · Roberto Castaneda-Gaxiola[3] · Ángel Iván Rubio-Gayosso[4] · Guillermo Ceballos[4] · Juan Arcadio Molina-Guarneros[5]

Received: 8 October 2019 / Accepted: 3 December 2019 / Published online: 18 December 2019

Abstract

Background Deep vein thrombosis (DVT) is a common complication during postoperative convalescence characterized by hypercoagulability, vascular endothelium damage and blood stasis. It increases noticeably in peri/postoperative phases of surgery procedures. Pulmonary embolism secondary to iliofemoral DVT is a frequent cause of death.

Methods Adult patients scheduled for plastic and reconstructive surgery (PRSx) with moderate to high thrombogenic risk were selected. We evaluated the efficacy and safety of bemiparin compared to enoxaparin as chemoprophylaxis for DVT. Following balanced general anesthesia techniques, patients were randomly assigned for subcutaneous enoxaparin 40 IU (Group-E) or bemiparin 3500 IU (Group-B) q24h starting 6 h after procedure conclusion for at least 10 days. All patients were evaluated for DVT through Doppler ultrasound mapping of the lower limbs.

Results Seventy-eight patients were evaluated, mostly women (83%), physical status ASA II (59%), ASA III (10%); Caprini's thrombogenic risk score 3–4 (moderate) 58%, 5–6 (high) 29%, > 6 (too high) 13%; demographics, clinical variables and scores were similar between groups. Median drainage time in breast surgery was 4 days in both groups ($p = 0.238$). In the case of abdominal surgery, median was 14 days in Group-E versus 13 days in Group-B ($p = 0.059$). No DVT was detected in either group.

Conclusions DVT was prevented with bemiparin, without significant bleeding increase nor adverse events; moreover, the cost of bemiparin is lower than enoxaparin. Bemiparin can be considered as alternative drug for DVT chemoprophylaxis in PRSx procedures.

Level of Evidence III This journal requires that authors assign a level of evidence to each article. For a full description of these Evidence-Based Medicine ratings, please refer to the Table of Contents or the online Instructions to Authors www.springer.com/00266.

Keywords Deep venous thrombosis · Chemoprophylaxis · Bemiparin · Enoxaparin · Plastic surgery

Introduction

Anesthesia and surgery induce a prothrombotic state, while surgery also triggers an inflammatory response. These factors may result in a state of hypercoagulability, mainly in predisposed patients such as those who carry factor V Leiden. DVT is a common and potentially lethal complication in the perioperative period. The pathophysiology of

✉ Juan Arcadio Molina-Guarneros
jamg@unam.mx

1 Anesthesiology Service, American British Cowdray Santa Fe Medical Center, No. 154 Carlos Graef Fernandez Av., Santa Fe, Del. Cuajimalpa, 053333 Mexico City, Mexico

2 Plastic and Reconstructive Surgery, ABC Santa Fe Medical Center, No. 154 Carlos Graef Fernandez Av., Santa Fe, Cuajimalpa, 053333 Mexico City, Mexico

3 Angiology and Vascular Surgery, ABC Santa Fe Medical Center, No. 154 Carlos Graef Fernandez Av., Santa Fe, Cuajimalpa, 053333 Mexico City, Mexico

4 Sección de Estudios de posgrado, Escuela Superior de Medicina, Instituto Politécnico Nacional, Plan de San Luis y Díaz Mirón, CP 11340 Mexico City, Mexico

5 Pharmacology Department, Faculty of Medicine, National Autonomous University of Mexico, Av. Universidad No. 3000, Colonia Ciudad Universitaria, CP 04510 Alcaldía Coyoacan, Mexico City, Mexico

this process is related to alterations of the Virchow's triad in the peri- and postoperative phases. Venous thromboembolism (VTE) begins with DVT, which is generated in the deep veins of the leg (calf) or pelvis [1]. In some cases, DVT detaches from the vein and moves to the right side of the heart and from there to the pulmonary arteries resulting in pulmonary embolism (PE) [2]. Certain factors predispose patients to develop VTE, including surgery, trauma, hospitalization, immobilization, pregnancy, oral contraceptives, cancer, long non-stop travel, advanced age, obesity, smoking, major medical illness (such as diabetes mellitus, arterial hypertension, chronic inflammatory bowel disease), autoimmune diseases (such as systemic lupus erythematosus and antiphospholipid antibody syndrome) or previous VTE [3, 4] which may also be induced by a genetic component [5]. The main cause of death is due to PE secondary to iliofemoral DVT [6, 7]. DVT and PE are the main causes of morbidity and mortality in the medical and surgical patient, this situation occurs because DVT is frequently asymptomatic, poorly diagnosed, and unrecognized until death; moreover, there is a lack of routine postmortem examinations, and the global public awareness is substantially lower for PE (54%) and DVT (44%) than for heart attack (88%) and stroke (85%) [8]. All these factors result in a marked underestimation of DVT incidence. In the UK, it is responsible for more than 25,000 deaths annually, and it is estimated that throughout Europe the total number of VTE cases amounts to 1,100,000 [9]. In the USA, there are more than 5 million events with a PE incidence of 500 thousand cases annually [10] and a mortality of 200,000 cases [11]. Some data suggest that the incidence of DVT in Mexico is 200,000 cases per year, with a mortality of 10% in patients with previous heart disease [12]. Sigler-Morales et al. [13] from La Raza Medical Center of the Mexican Institute of Social Security (IMSS) in Mexico City reported 15% of PE in 1685 autopsy studies, as a direct cause of death by 20% and indirectly by 62%.

Bemiparin is indicated for the acute treatment of DVT with or without PE, for VTE prophylaxis in surgical and non-surgical patients, and for the prevention of coagulation in the extracorporeal circuit during hemodialysis. Considering the aforementioned conditions summed to the particular lack of Mexican studies on the pharmacological prophylaxis of DVT in PRSx patients, we decided to compare the efficacy and safety of bemiparin, a second-generation low molecular weight heparin (LMWH), with enoxaparin, a first-generation LMWH as reference standard in our country.

Materials and Methods

Eighty patients were enrolled between July 2016 and April 2018. We carried out an unblinded sequential list trial (assigning every incoming individual to a different group with respect to the previous patient) involving two parallel treatments in Group-E (enoxaparin) and Group-B (bemiparin). The present study complied with the Declaration of Helsinki and the General Health Law of Mexico. Approval and authorization were obtained from the Ethics and Research Committee on human research of the ABC Medical Center in Mexico City. The study was registered on http://www.isrctn.com/ Registration ID: International Standard Randomised Controlled Trial Number: ISRCTN (13851176). Registered (27/08/2019).

Seventy-eight individuals were analyzed (39 patients for each group) (Fig. 1).

Adult patients (age equal or over 18 years old) were evaluated after signing their informed consent. Both genres were included. Patients were scheduled for major PRSx procedures involving moderate to high thrombogenesis risk (3 points or more) according to Caprini's classification [14], which has been validated for surgical procedures by the American College of Chest Physicians (ACCP), for procedures of plastic and reconstructive surgery by the American Society of Plastic Surgery (ASPS) [15]. Patients reported a physical condition in accordance with the American Society of Anesthesiologists (ASA) between grades I and III. Exclusion criteria encompassed active bleeding, heparin-induced thrombocytopenia, platelets count less than 100,000, severe renal impairment, coagulopathy, recent intracranial surgery, epidural anesthesia or lumbar puncture during the last 24 h. Preoperative examinations included blood count, blood chemistry, coagulation tests and electrocardiogram. DVT assessment was performed before and after surgery using USG Sonosite Doppler Micromax and multifrequency linear transducer from 4 to 12 MHz, ultrasound study of pelvic limbs in transversal and longitudinal sections, obtaining images in both gray scale and color, with Valsalva maneuvers and compression in all superficial and deep veins, looking for thrombosis or reflux at key points. All patients received general balanced anesthesia induced with propofol 2 mg/kg, fentanyl 2 μg/kg and rocuronium 600 μg/kg. This was sustained with a continuous intravenous infusion of fentanyl and the inhalation of desflurane or sevoflurane and fractionated neuromuscular blocker upon request. Intraoperative monitoring included continuous electrocardiogram, flow-velocity curves, non-invasive blood pressure, pulse oximetry, end-tidal CO_2, bispectral index, body temperature, and vigilance of the neuromuscular blockade by the train of four test. Six hours after the end of the surgical

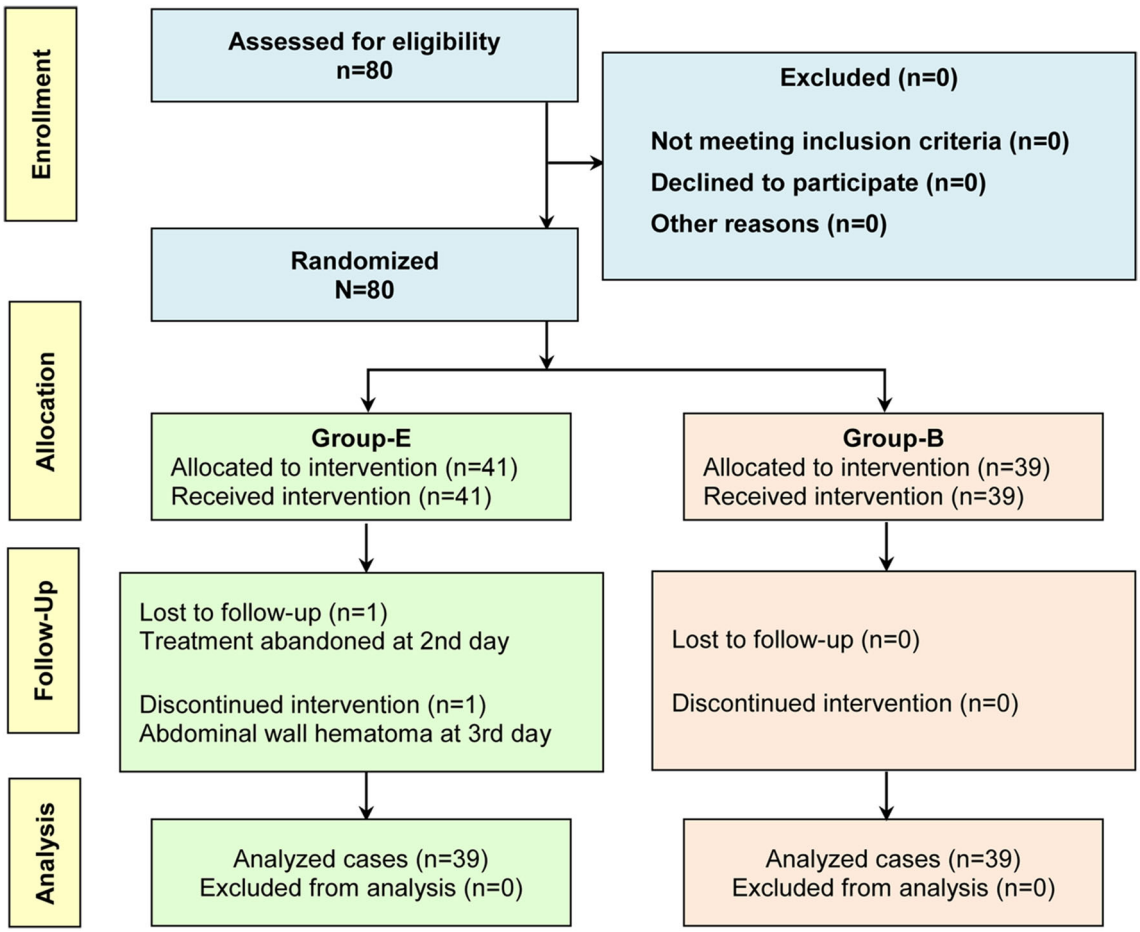

Fig. 1 CONSORT flow diagram of the trial sample

procedure patients were assigned according to a sequential list for subcutaneous administration of enoxaparin 40 IU (Group-E) or bemiparin 3500 IU (Group-B) every 24 h (q24h). LMWH treatment was delivered during at least 10 days. Postoperative bleeding was also quantified through surgical drains.

Results

Demographic data and previous medical history are shown in Table 1. Patients were prevalently female (83%). We found 15 cases (19.23%) with inherited or acquired thrombophilia disorders. Median age of Group-E was 51 versus 49 in Group-B ($p = 0.916$). Baseline weight and body mass index (BMI) were also similar between groups; Preexisting pathologies in the enoxaparin group were led by cardiovascular diseases (43.58%), followed by gastrointestinal diseases (30.76%), chronic lung disease (28.20%), depression (25.64%), thyroid disease and obesity (17.94% each), thrombophilia (11.53%), diabetes and cancer (5.12% each). In the bemiparin group, chronic lung disease (33.3%) was the first, followed by cardiovascular diseases (23.7%), gastrointestinal diseases and depression (15.38%), thyroid diseases (12.82%), cancer, obesity and thrombophilia (7.69%), diabetes (5.12%) and chronic renal failure (2.56%). Comparisons between groups showed no statistical differences on medical history pathologies (Table 1).

Physical status score categories for the whole sample were ASA I (31%), ASA II (59%), and ASA III (10%); Caprini's thrombogenic risk score was moderate (3–4 points, 58%), high (5–6 points, 29%), and higher (> 6 points, 13%). Surgery and anesthesia lengths as well as surgery types were statistically similar between groups. The most frequent kind of surgery was breast surgery (36%), followed by combined surgery (24.3%), head and neck (18%), abdominoplasty (11.5%), and liposuction (10%). It should be noted that all patients presented a mild to moderate increase in postoperative bleeding quantified through surgical drains, which was not clinically significant. Breast surgery cases reported a median drain persistency of 4 days, while abdominal surgery patients reported 14 (Table 2). Doppler scanning of the lower limbs reported

Table 1 Baseline demographics and medical history

Characteristics	Group-E (n = 39)	Group-B (n = 39)	p
Gender, women	32 (82.05%)	33 (84.61%)	0.761*
Age (years)	51.00 (41.25–62.00)	47.00 (42.00–61.00)	0.916*
Weight (kg)	65.00 (54.00–77.75)	62.00 (56.00–70.00)	0.610*
BMI (kg/m^2)	23.00 (21.00–29.75)	23.00 (21.25–25.00)	0.482*
Cardiovascular disease	17 (43.58%)	9 (23.07%)	0.055**
Gastrointestinal disease	12 (30.76%)	6 (15.38%)	0.107**
Chronic lung disease	11 (28.20%)	13 (33.33%)	0.624**
Depression	10 (25.64%)	6 (15.38%)	0.262**
Thrombophilia	9 (11.53%)	6 (7.69%)	0.389**
Obesity	7 (17.94%)	3 (7.69%)	0.176**
Thyroid disease	7 (17.94%)	5 (12.82%)	0.530**
Diabetes	2 (5.12%)	2 (5.12%)	1.000$^+$
Cancer	2 (5.12%)	3 (7.69%)	1.000$^+$
Chronic renal failure	0 (0.00%)	1 (2.56%)	1.000$^+$

Data are expressed as median and percentiles (25th–75th) for quantitative variables; frequencies and proportions (%) are shown for qualitative variables

BMI body mass index, *dis* disease

*Mann–Whitney Rank Sum Test, **Chi-squared test, $^+$Fisher' exact test

Table 2 Evaluation scores and surgery characteristics

Categories	Group-E (n = 39)	Group-B (n = 39)	p
Physical status ASA I	12 (30.76%)	12 (30.76%)	1.000**
ASA II	22 (56.41%)	24 (61.53%)	0.645**
ASA III	5 (12.82%)	3 (7.69%)	0.712**
Risk Caprini 3–4 points	19 (48.72%)	25 (64.10%)	0.171**
≥5 points	20 (51.28%)	14 (35.89%)	0.513**
Surgical time (min)	235.00 (166.25–285.00)	225.00 (190.00–277.50)	0.857*
Anesthetic time (min)	260.00 (196.25–320.00)	255.00 (210.00–303.75)	0.799*
Type of surgery			
Breast	12 (30.76%)	16 (41.02%)	0.345**
Abdominal	2 (5.12%)	7 (17.94%)	0.154**
Liposuction	5 (12.82%)	3 (7.69%)	0.712**
Head and neck	8 (20.51%)	6 (15.38%)	0.555**
Combined	12 (30.76%)	7 (17.94%)	0.187**
Drainages time (days)			
Breast	4 (3.50–4.00)	4 (3.00–4.00)	0.238*
Abdominal	14 (14.00–14.00)	13 (12.00–13.25)	0.059*

Data are expressed as frequencies and proportions (%) for qualitative variables; median and percentiles (25th–75th) are shown for quantitative variables

ASA American Society of Anesthesiologists

*Mann–Whitney Rank Sum Test, **Chi-squared test

no abnormalities in neither deep veins nor the arterial system of any patient. One patient from the enoxaparin group presented abdominal wall hematoma twelve hours after an abdominoplasty, which required surgical drainage. Anticoagulant therapy was suspended on the third day, and there was no subsequent complication. Another male patient from the same group abandoned the treatment on the second day; both cases were eliminated from the analysis.

Thrombophilia types among fifteen diagnosed patients were predominantly present in women (93%). The most frequent diagnosis was unspecified thrombophilia (40%),

followed by hyperhomocysteinemia (20%), while the remaining thrombophilia types showed 13% each. No statistical differences were found between groups (Table 3).

We have summarized the last 8 years of reports on interventions with either low molecular weight heparin LMWH or unfractionated heparin UFH involving moderate to high thrombogenesis risk (3 ≥) according to Caprini's classification over several plastic surgery procedures and their implication in DVT, PE, and hematoma development [16–23] (Table 4).

Discussion

Plastic and reconstructive surgery, together with major orthopedic surgery, oncological surgery, and pelvic surgery, presents the highest thrombogenic incidence in the surgical patient. According to the ACCP, a third of the 200,000 annual deaths related to DVT occur after surgical events [24]. In 2001, the ASPS estimated that there were annually 18,000 cases of DVT in patients undergoing PRSx procedures, varying between 0.5 and 2% [25]. While this rate may seem low, these numbers only represent symptomatic patients, and about two thirds of patients with DVT are clinically asymptomatic, leading to a substantial delay in diagnosis and treatment [26]. During the last two decades, there has been a remarkable increase in PRSx due in part to the need of the young adult population (mostly female) to improve their personal image and increase their self-esteem. According to a survey by the International Society of Aesthetic Plastic Surgery, Mexico ranks third in PRS demand in the Americas and fourth overall worldwide [27]. Defective adherence to globally accepted prophylaxis guidelines is unfortunately the main cause of thromboembolism. A large number of reports in Canada and the USA have shown that 68% of VTE cases did not receive prophylaxis [28, 29]. The severity of this condition is such that of all patients undergoing surgery of any kind without thromboprophylaxis, almost a fifth presents asymptomatic DVT; among these, 90% of thrombi spontaneously lysed and 10% may present PE, resulting in a 30% mortality within the event's first hour [28]. In PRSx procedures, the incidence of VTE among patients undergoing head and neck surgery is 27.5%, among burned patients 23%, 4.2% in abdominoplasty patients, 1.32% in breast reconstruction surgery, and 0.59% in liposuction patients [30]. VTE results in a significant health burden, requiring prolonged anticoagulant therapy, and carries a substantial risk of post-thrombotic syndrome, post-thrombotic chronic pulmonary hypertension, and VTE recurrence. The annual mortality rate after a VTE event rises up between 20 and 25% [31].

More than 40 years ago, the classic multicenter reference study conducted by Kakkar et al. (1975), across 28 medical centers in more than 4000 surgical patients demonstrated that small doses of ultra-fractionated heparin (UFH), reduced the DVT rate from 24.7% in the placebo group to 7.7% in the heparin group with a corresponding reduction in fatal PE from 0.8 to 0.1% [32]. Even more remarkable was the meta-analysis conducted by Collins 13 years later among 13,000 patients in 70 medical centers, which reaffirmed the results of the original study; the incidence of DVT was reduced from 22.4 to 9% by the administration of UFH in patients of general, gynecological, orthopedic and urological surgery, where once again the incidence of fatal PE was reduced from 0.9% in the control group to 0.3% in the heparin group [33]. Seventeen years later (2005), Haas et al. reported the results of a double-blind randomized comparative study between UFH and LMWH (certoparin) in 23,078 surgical patients, demonstrating that the incidence of fatal PE was 0.15% [34]. Throughout all these years, multiple consensus conferences have concluded that high-risk surgical patients

Table 3 Thrombophilia types

Characteristics	Group-E (n = 9)	Group-B (n = 6)	p
Gender, women	9 (100%)	6 (83.3%)	0.143*
Type of thrombophilia			
[a]AFS	1 (11.1%)	1 (16.6%)	1.000[+]
Factor V Leiden	1 (11.1%)	1 (16.6%)	1.000[+]
[b]HHC	1 (11.1%)	2 (33.3%)	1.000[+]
Mutation MTFHR	1 (11.1%)	1 (16.6%)	1.000[+]
UT	4 (44.4%)	2 (33.3%)	0.651*
[c]SEL	1 (11.1%)	1 (16.6%)	1.000[+]

Data are expressed as frequencies and proportions (%)

AFS antiphospholipid syndrome, *HHC* hyperhomocysteinemia, *MTFHR* methylenetetrahydrofolate reductase, *UT* unspecified thrombophilia, *SLE* systemic lupus erythematosus

*Chi-squared test, [+]Fisher' exact test

[a,b,c]One patient in Group-B has AFS, HHC, SEL

Table 4 Studies on deep vein thrombosis prophylaxis in plastic and reconstructive patients

References	Type of study	No. participants	Intervention	Outcomes		
				DVT	PE	Hematoma
Hatef [16]	Prospective cases and controls	360 Excisional body contouring patients caprini ≥ 3	LMWH 30 mg twice daily+			
			SCD (n = 137)	4.38%		7.3%
			SCD (n = 221)	5.88%		0.5%
Seruya [17]	Retrospective cohort	120 Patients of plastic surgery caprini > 4	IPC/ES (n = 48)			
			IPC/ES + ASA (n = 24)			
			LMWH or UHF + IPC/ES (n = 60)	6.7%	0.8%	12.5%
			LMWH or UHF+			
			IPC/ES + ASA (n = 26)			
Panucci [18]	Retrospective cohort multicentric	1458 Patients of plastic surgery caprini ≥ 3	Enoxa 40 mg. daily	↓0.61% to 0.32%[a] (DVT)		
				=1.22% to 1.20%[b] (DVT)		
			Enoxa 30 mg twice daily (BMI > 40)	↓2.55% to 1.15%[c] (DVT)		
				↓8.54% to 4.07%[d] (DVT)		
Panucci [19]	Retrospective cohort multicentric	3681 Patients of plastic surgery caprini ≥ 3	LMWH 40 mg. once daily or 30 mg Twice daily (BMI > 40) +SCD (n = 1567)			3.38%
			SCD (n = 2114)			2.65%
Keith [20]	Retrospective cohort multicentric	300 Breast reconstruction with free flap or tissue expander	LMWH 30 mg +			
			SCD (n = 137)			4.5%
			SCD (n = 221)			2.5%
Michaels [21]	Retrospective cohort multicentric	546 Body contour surgery in the massive weight loss patient	LMWH 30 mg twice daily + SCD (n = 212)		0.18%	6.60%
			SCD (n = 334)			4.57%
Campbell [22]	Retrospective cohort	151 Abdominoplasty surgery	Enoxa 40 mg Twice daily + SCD (n = 50)			
			UFH 5000 U. + SCD (n = 101)			1%
Konoeda [23]	Prospective cases and controls	35 Patients with breast reconstruction	IPC/ES (n = 35)	31.4%	0.35%	

IPC intermittent pneumatic compression; *ES* elastic stockings; *ASA* acetylsalicylic acid; *LMWH* low molecular weight heparin; *UHF* unfractionated heparin; *SCD* Sequential compression device; *BMI* body mass Index; *Enoxa* enoxaparina; *DVT* deep vein thrombosis; *PE* pulmonary embolism

[a]Caprini 3–4

[b]Caprini 5–6

[c]Caprini 7–8

[d]Caprini > 8

should be protected with anticoagulants. The latest consensus guidelines (2012) indicate that the incidence of DVT without prophylaxis rates between 40 and 80% while PE rises up to 5% in some of these patients without prophylaxis [24, 35, 36]. It should be assumed that after all these years and considering the evidence accumulated around the world, DVT prophylaxis should be uniformly administered in high-risk surgical patients. A decade ago, the multinational multicenter study ENDORSE was conducted in 358 hospitals across 32 countries where a sample of 30,827 surgical patients revealed that 64% were at risk of developing DVT and only 59% received adequate antithrombotic prophylaxis [37]. DVT prevention remains an important issue within the plastic surgery community; however, there is little consensus about its prophylaxis regarding patients undergoing the most common surgical procedures. Bemiparin is a second-generation LMWH that has been less studied respect to heparin. It has been used in Europe, reported in a study conducted by Kakkar et al. in 298 patients with total hip replacement who were randomized to receive 3500 U of bemiparin every 24 h or 5000 U of UFH twice a day, two hours before surgery and continuously for 8–12 days. Bemiparin showed greater efficacy when evaluated through venography and a safety profile similar to UFH [38]. Even though this study was performed on orthopedic surgery, we used the same dosage of 3500 U every 24 h and observed no thrombotic effect while using venous Doppler instead of venography. In

another multicenter study performed by Navarro et al. in 381 patients receiving a total knee prosthesis, 2 groups were randomized to receive either 3500 U of bemiparin 6 h after surgery, or 40 U of enoxaparin 12 h before surgery. These dosages were then sustained every 24 h. The incidence of DVT was 32.1% in the bemiparin group and 36.9% in the enoxaparin group, the difference in absolute risk was of 4.6% in favor of bemiparin, significant bleeding was observed in 3 patients of each group, and no deaths were reported. This study showed that bemiparin is as effective in the postoperative period as enoxaparin before surgery in the prevention of DVT [39]. Moreover, bemiparin was employed at the same dosage, administration timing, and duration. In our study, such differences in favor of bemiparin were not observed; nevertheless, we also did not observe any of the significant bleeding with either anticoagulant. In another report by Sayed, 100 critically ill patients at high DVT risk were assigned to receive 3500 U of bemiparin or 40 U of enoxaparin and were followed for 60 days. DVT confirmation was observed in 2 bemiparin patients (4%) and 10 enoxaparin patients (20%) ($p < 0.05$). PE was documented in 7 patients (14%) of the enoxaparin group and no case in the bemiparin group ($p < 0.05$); no deaths were reported in any group [40]. In 2014, a study by Briones et al. from the General Hospital of the Secretary of Health in Mexico City enrolled obstetric patients in critical condition at high DVT risk of; 25 patients received 3500 daily units of bemiparin during their internment; none presented DVT and there were no deaths or adverse effects. Researchers concluded that the pharmacological profile of bemiparin allows its consideration as a first-line drug [41]. While these two studies reported similar effects at the same dose of bemiparin as ours, they cannot be compared to it since no surgical procedure was involved in either of them. In our study, there was no documented presence of DVT presented by any patient in either group; only one patient in the enoxaparin group (2.56%) presented an abdominal wall hematoma after an abdominoplasty that required surgical drainage. Undoubtedly, additional research is required in both plastic and reconstructive surgery and other surgical specialties to add more clinical evidence on the usefulness of bemiparin as an alternative drug in the prophylaxis and treatment of patients with a high risk of DVT. Castañeda et al. conducted a retrospective cohort trial aiming to detect patients with thrombophilia at the ABC Medical Center in Mexico City. They found that, in a period of 6 years, 3010 out of 15,485 thrombophilia studies performed on 3893 patients were positive (19.4%). This high rate of positive cases may be explained by the individuals' characteristics: they were high-risk patients [42]. In our study, we found a similar incidence of (19.23%) thrombophilia disorders. Perhaps this is associated with the genetic background of our hospital's population where European components are much less mixed with others (thrombophilia being a rare disease among the larger Mestizo population of our country). This could be an epidemiological finding in need of future studies to verify it. Finally, there is not enough clinical evidence to suggest a recommendation on the optimal duration of thromboprophylaxis using LMWH. Based on the results of some randomized double-blind clinical trials that have shown the efficacy and safety of LMWH in preventing DVT and PE, they are currently widely recommended for inpatient hospital use [43–45]. However, in some patients, the risk of DVT may persist for a few weeks [46–48] after having been discharged from the hospital, such as patients undergoing pelvic or abdominal cancer surgery who are in a twofold increased risk of developing DVT, and three times higher of developing fatal PE as compared to patients without cancer in similar surgeries [49, 50]. A meta-analysis of three randomized trials, one double-blind and two open trials, which included 1104 patients with and without cancer, showed that patients who received extended thromboprophylaxis with LMWH for one month reported a significant reduction in proximal and total DVT when compared to patients who received only thromboprophylaxis within the hospital [51]. Additional clinical evidence was reported by Kakkar et al. in a multicenter randomized double-blind study on 626 patients undergoing abdominal and pelvic cancer surgery who received 3500 U of bemiparin once a day for 8 days. They were randomized in 2 groups, where one group received bemiparin and the other a placebo for another 20 days; relative risk reduction was observed in the group of bemiparin by 82.4% (95% CI 21.5–91.6%, $p = 0.010$), with no significant increase in bleeding complications [52]. A study conducted in the USA in 2011 by Clavijo-Alvarez et al., 4081 surveyed registered members of the American Society of Plastic Surgery via e-mail; 596 complete answers were received (14.6%). Out of the participant plastic surgeons, 83% practiced privately, whereas 17% did so academically. DVT was reported by 40% of the inquired surgeons, 34% reported PE, and 7% reported having had one death imputable to PE during the postoperative period; 39% to 48% reported not having administered any DVT prophylaxis whatsoever to their patients. The most common reason for not including any routine prophylaxis was the fear of bleeding (84%), followed by the lack of specific evidence in the practice of plastic surgery. Academic surgeons used more chemoprophylaxis when compared with non-academic ones ($p < 0.05$) [53]. A similar study was conducted in Denmark in 2016 by Nielsen et al., through an e-mail survey in 42 clinics (8 public and 34 private sites); all public and 13 private clinics answered the survey. Overall, 89% of participants declared they had guidelines for DVT prophylaxis (100% of public clinics, 85% private). The most frequent prophylaxis measures are an

adequate position, compression through elastic stockings, and early mobilization (68%).None reported the use of intermittent pneumatic compression stockings. The most recurrent pharmacological prophylaxis administered LMWH in the postoperative period (37%), followed by preoperative administration (21%). All public institutions reported using pharmacological prophylaxis while only half of the private ones did so (54%); four private clinics mentioned the use of other modalities. In those cases where DVT prophylaxis was absent, arguments were similar to those reported in the USA: fear of bleeding, lack of evidence in plastic surgery, and also some financial aspects. More than a quarter of the participant surgeons (26%) reported dealing with at least one DVT case over the last 5 years, 33% in public clinics and 23% in private clinics, but no deaths at all [54]. The research asserted that the risk of DVT in plastic surgery should not be ignored and that conclusive evidence is necessary to establish risk stratification models as well as implementing institutional prophylaxis plans. In the ABC Medical Center in Mexico City, which is a private institution, our specific surgical team followed the recommendations of DVT prophylaxis issued by the consensus of the American College of Chest Physicians (ACCP) in the year 2012 [24]. Enoxaparin treatment was considered as the best comparative intervention, being the first-generation LMWH in our country which has been widely studied around the world in different clinical scenarios during the last three decades. Table 4 includes the only case/control prospective study on DVT chemoprophylaxis with enoxaparin (Hatef, 2008) [16], where only abdominoplasty patients reported a significant difference (no thrombosis whatsoever) respect to the control group. This is consistent with our results on thrombogenic events (none) when using enoxaparin. There are no Bemiparin reports on plastic surgery patients to be compared with our data.

Although there is a consensus about sustained anticoagulation in high-risk patients, future studies are necessary to determine an optimal time range to maintain pharmacological prophylaxis in these patients. Thromboembolic disease is the leading cause of morbidity and mortality in hospitalized surgical and non-surgical patients worldwide. Despite the fact that, over the last decades, multiple studies have reported information related to the epidemiology, detection, prophylaxis, and treatment of DVT in surgical patients, a significant proportion of surgeons still refrain from adequate protection to patients at high DVT risk. Numerous studies have shown that the use of adequate thromboembolic prophylaxis is safe and effective both therapeutically and financially. In spite of this evidence, DVT prophylaxis is often far from adequate, which is why it is necessary to adopt thrombogenic risk assessment scales at an institutional level in all hospitalized surgical patients (Caprini) and also non-surgical patients (Padua), in order to implement prophylaxis protocols to reduce the high rates of morbidity and mortality that largely affect them still. The degree of anticoagulation and the duration of prophylaxis remain as problems to implement antithrombotic therapy guidelines due to the low awareness regarding postoperative thrombosis risks, in addition to concerns upon bleeding and the complexity of anticoagulation with available drugs. There are currently multiple methods and therapeutic options to treat different DVT risk degrees, which imply small but important differential effects to consider. Anticoagulants increase the risk of bleeding, so it is necessary to adapt treatment strategies incorporating etiology, risk, benefit, cost and patient preference; although great progresses have been made, further studies are necessary to understand the individual risks of patients to make ideal treatment decisions.

Conclusions

In this study, bemiparin performed adequately against DVT during the immediate postoperative period in patients at moderate to high thrombogenic risk undergoing PRSx procedures. This performance included no clinically significant increase in postoperative bleeding, and there were no adverse effects. All patients were comfortable with the subcutaneous administration of the drug; its cost–benefit ratio makes it a serious competitor respect to enoxaparin. Bemiparin can be considered as an alternative drug to prevent DVT in PRSx patients at significant thrombogenic risk. Although there is controversy in the literature over chemoprophylaxis in outpatients, based on the results of our study and other authors' recommendations, we are convinced such patients should receive this treatment. Each patient should be medicated taking into account thrombogenic risk, personal background, clinical condition, and the kind of procedure to be performed.

Acknowledgements The authors declare that they have no conflict of interest. The present study was conducted within the Medical Research Doctoral Program of the National Politechnical Institute's Superior School of Medicine (Doctorado en Investigación en Medicina, Escuela Superior de Medicina, Instituto Politécnico Nacional).

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest. None of the authors was paid to include any patient in this study. No sponsoring company paid for any of the medications included in this study. No professional writing service was hired to compile this report. The study was conducted without any public or private grant. No patient or physician was paid to take part in the study.

Ethical Approval Authors declare that the study has been approved by the appropriate institutional and/or national research ethics committee and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed Consent All patients included in this study signed their informed consent to participate.

References

1. Kearon C (2003) Natural history of venous thromboembolism. Circulation. https://doi.org/10.1161/01.CIR.0000078464.82671.78
2. Piazza G, Goldhaber SZ (2006) Acute pulmonary embolism: part I: epidemiology and diagnosis. Circulation 114(2):e28–e32
3. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd (2000) Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med 160(6):809–815
4. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ 3rd (2005) Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med 143(10):697–706
5. Larsen TB, Sorensen HT, Skytthe Johnsen SP, Vaupel JW, Christensen K (2003) Major genetic susceptibility for venous thromboembolism in men: a study of Danish twins. Epidemiology 14(3):328–332
6. Hunt BJ (2009) The prevention of hospital-acquired venous thromboembolism in the United Kingdom. Br J Haematol 144(5):642–652
7. Zhu TI, Martinez J (2009) Emmerich, venous thromboembolism: risk factors for recurrence. Arterioscler Thromb Vasc Biol 29(3):298–310
8. Wendelboe AM, Raskob GE (2016) Global burden of thrombosis: epidemiologic aspects. Circ Res 118(9):1340–1347
9. Cohen AT, Agnelli G, Anderson FA, Arcelus JI, Bergqvist D, Brecht JG, Greer IA, Heit JA, Hutchinson JL, Kakkar AK, Mottier D, Oger E, Samama MM, Spannagl M, VTE Impact Assessment Group in Europe (VITAE) (2007) Venous thromboembolism (VTE) in Europe The number of VTE events and associated morbidity and mortality. Thromb Haemost 98(4):756–764
10. Carrier M, Le Gal G, Wells PS, Rodger MA (2010) Systematic review: case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism. Ann Intern Med 152(9):578–589
11. Tagalakis V, Patenaude V, Kahn SR, Suissa S (2013) Incidence of and mortality from venous thromboembolism in a real-world population: the Q-VTE Study Cohort. Am J Med 126(9):832e13–21
12. Pulido T, Aranda A, Zevallos MA, Bautista E, Martinez-Guerra ML, Santos LE, Sandoval J (2006) Pulmonary embolism as a cause of death in patients with heart disease: an autopsy study. Chest 129(5):1282–1287
13. Sigler-Morales L, Romero T, Meillón LA, Gutiérrez L, Aguirre García J, Esparza C (1996) Pulmonary thromboembolism in autopsies over 10 years. Rev Med Inst Mex Seguro Soc 34:7–11
14. Caprini JA (2005) Thrombosis risk assessment as a guide to quality patient care. Dis Mon. https://doi.org/10.1016/j.disamonth.2005.02.003
15. Pannucci CJ, Bailey SH, Dreszer G, Fisher Wachtman C, Zumsteg JW, Jaber RM, Hamill JB, Hume KM, Rubin JP, Neligan PC, Kalliainen LK, Hoxworth RE, Pusic AL, Wilkins EG (2011) Validation of the Caprini risk assessment model in plastic and reconstructive surgery patients. J Am Coll Surg. https://doi.org/10.1016/j.jamcollsurg.2010.08.018
16. Hatef DA, Kenkel JM, Nguyen MQ, Farkas JP, Abtahi F, Rohrich RJ, Brown SA (2008) Thromboembolic risk assessment and the efficacy of enoxaparin prophylaxis in excisional Body contouring surgery. Plast Reconstr Surg 122:269–279
17. Seruya M, Venturi ML, Iorio ML, Davison SP (2008) Efficacy and safety of venous thromboembolism prophylaxis in highest risk plastic surgery patients. Plast Reconstr Surg. https://doi.org/10.1097/PRS.0b013e31818dbffd
18. Panucci CJ, Dreszer G, Wachtman CF, Bailey SH, Portschy PR, Hamill JB, Hume KM, Hoxworth RE, Rubin JP, Kalliainen LK, Pusic AL, Wilkins EG (2011) Postoperative enoxaparin prevents symptomatic venous thromboembolism in high risk plastic surgery patients. Plast Reconstr Surg 128:1093–1103
19. Panucci CJ, Watchman CF, Dreszer G, Bailey SH, Portschy PR, Hamill JB, Hume KM, Hoxworth RE, Kalliainen LK, Rubin JP, Pusic AL, Wilkins EG (2012) The effect of postoperative enoxaparin on risk for re-operative hematoma. Plast Reconstr Surg 129:160–168
20. Keith JN, Chong TW, Davar D, Moore AG, Morris A, Gimbel ML (2013) The timing of prophylaxis low-molecular-weight-heparin administration in breast reconstruction. Plast Reconstr Surg 132:279–284
21. Michaels J, Coon D, Mulvey CL, Rubin JP (2015) Venous thromboembolism prophylaxis in the massive weight loss patient: relative risk of bleeding. Ann Plast Surg 74:699–702
22. Campbell W, Pierson J, Cohen-Shohet R, Mast BA (2014) Maximizing chemoprophylaxis against venous thromboembolism in abdominoplasty patients with the use of preoperative heparin administration. Ann Plast Surg. https://doi.org/10.1097/SAP.0000000000000132
23. Konoeda H, Yamaki T, Hamahata A, Ochi M, Osada A, Hasegawa A, Kirita M, Sakurai H (2016) Incidence of deep vein thrombosis in patients undergoing breast reconstruction with autologous tissue transfer. Phlebology. https://doi.org/10.1177/0268355516680427
24. Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, Samama CM (2012) Prevention of VTE in nonorthopedic surgical patients: antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141(2 Suppl):e227S–e277S
25. Young VL, Watson ME (2006) The need for venous thromboembolism (VTE) prophylaxis in plastic surgery. Aesthet Surg J. https://doi.org/10.1016/j.asj.2006.02.001
26. Campbell W, Pierson J, Cohen-Shohet R, Mast BA (2014) Maximizing chemoprophylaxis against venous thromboembolism in abdominoplasty patients with the use of preoperative heparin administration. Ann Plast Surg. https://doi.org/10.1097/SAP.0000000000000132
27. Campbell CA, Restrepo C, Navas G, Vergara I, Peluffo L (2019) Plastic surgery medical tourism: a review of 658 international patients and 1,796 cosmetic surgery procedures. Plast Reconst Surg Glob Open. https://doi.org/10.1097/GOX.0000000000002233
28. Goldhaber SZ, Bounameaux H (2012) Pulmonary embolism and deep vein thrombosis. Lancet 379(9828):1835–1846
29. Cohen AT, Tapson VF, Bergmann JF, Goldhaber SZ, Kakkar AK, Deslandes B, Huang W, Zayaruzny M, Emery L, Anderson FA Jr. (2008) Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE STUDY): a multinational cross-sectional study. Lancet. https://doi.org/10.1016/s0140-6736(08)60202-0

30. Miszkiewicz K, Perreault I, Landes G, Harris P, Sampalis J, Dionyssopoulos A, Nikolis A (2009) Venous thromboembolism in plastic surgery: incidence, current practice and recommendations. J Plast Reconstr Aesthet Surg 62:580–588
31. Cohen AT, Tapson VF, Bergmann JF, Goldhaber SZ, Kakkar AK, Deslandes B, Huang W, Zayaruzny M, Emery L, Anderson FA Jr, Investigators ENDORSE (2008) Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. Lancet. https://doi.org/10.1016/S0140-6736(08)60202-0
32. Kakkar VV, Corrigan TP, Fossard DP, Sutherland I, Shelton MG, Thirlwall J (1975) Prevention of fatal postoperative pulmonary embolism by low doses of heparin. An international multicentre trial. Lancet 12(2):45–51
33. Collins R, Scrimgeour A, Yusuf S, Peto R (1988) Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. N Engl J Med 318(18):1162–1173
34. Haas S, Wolf H, Kakkar AK, Fareed J, Encke A (2005) Prevention of fatal pulmonary embolism and mortality in surgical patients: a randomized double-blind comparison of LMWH with unfractionated heparin. Thromb Haemost 94(4):814–819
35. Gallus AS, Hirsh J, O'Brien SE, McBride JA, Tuttle RJ, Gent M (1976) Prevention of venous thrombosis with small, subcutaneous doses of heparin. JAMA 235(18):1980–1982
36. Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, Ray JG (2004) Prevention of venous thromboembolism: the Seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 126(3 Suppl):338s–400s
37. Musial J, Sydor WJ, Investigators-Poland ENDORSE (2008) Venous thromboembolism risk and prophylaxis in the acute hospital care setting–results of the ENDORSE study in Poland. Pol Arch Med Wewn 118(10):555–561
38. Kakkar VV, Howes J, Sharma V, Kadziola Z (2000) A comparative double-blind, randomised trial of a new second generation LMWH (bemiparin) and UFH in the prevention of post-operative venous thromboembolism. The Bemiparin Assessment groupm. Thromb Haemost 83(4):523–529
39. Navarro-Quilis A, Castellet E, Rocha E, Paz-Jimenez J, Planes A (2003) Efficacy and safety of bemiparin compared with enoxaparin in the prevention of venous thromboembolism after total knee arthroplasty: a randomized, double-blind clinical trial. J Thromb Haemost 1(3):425–432
40. Abbas MS (2017) Bemiparin versus enoxaparin in the prevention of venous thromboembolism among intensive care unit patients. Indian J Crit Care Med. https://doi.org/10.4103/ijccm.IJCCM_23_17
41. Briones-Vega C, Viruez-Soto JA, Vallejo-Narváez CM, Nieto-Anaya NM, Briones-Garduño JC, Díaz-De León-Ponce MA (2014) Bemiparina en obstetricia crítica. Revista Mexicana de Anestesiología 37(4):266–270
42. Castañeda-Gaxiola R, Munive-Lima MR, Meillón-García LA, Rish-Fein L, Sigler-Morales L, Prieto-Olivares P (2017) Trombosis Venosa asociada a trombofilias. Revisión y reporte de casos. Revista Mexicana de Angiología 45(2):73–79
43. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, Colwell CW (2008) Prevention of venous thromboembolism: American college of chest physicians evidence-based clinical practice guidelines (8th edition). Chest 133(6 Suppl):381–453
44. Nicolaides AN, Fareed J, Kakkar AK, Breddin HK, Goldhaber SZ, Hull R, Kakkar VV, Michiels JJ, Myers K, Samama M, Sasahara A, Kalodiki E (2006) Prevention and treatment of venous thromboembolism. International consensus statement (guidelines according to scientific evidence). Int Angiol 25(2):101–161
45. Nicolaides AN, Fareed J, Kakkar AK, Comerota AJ, Goldhaber SZ, Hull R, Myers K, Samama M, Fletcher J (2013) Prevention and treatment of venous thromboembolism: international consensus statement (guidelines according to scientific evidence). Clin Appl Thromb Hemost 19(2):116–118
46. Lyman GH, Bohlke K, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, Balaban EP, Clarke JM, Flowers CR, Francis CW, Gates LE, Kakkar AK, Key NS, Levine MN, Liebman HA, Tempero MA, Wong SL, Somerfield MR, Falanga A (2015) Venous thromboembolism prophylaxis and treatment in patients with cancer: american society of clinical oncology clinical practice guideline update 2014. J Clin Oncol 33(6):654–656
47. Huber O, Bounameaux H, Borst F, Rohner A (1992) A postoperative pulmonary embolism after hospital discharge. An underestimated risk. Arch Surg. https://doi.org/10.1001/archsurg.1992.01420030076014
48. Agnelli G, Bolis G, Capussotti L, Scarpa RM, Tonelli F, Bonizzoni E, Moia M, Parazzini F, Rossi R, Sonaglia F, Valarani B, Bianchini C, Gussoni G (2006) A clinical outcome-based prospective study on venous thromboembolism after cancer surgery: the @RISTOS project. Ann Surg 243(1):89–95
49. White RH, Zhou H, Romano PS (2003) Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. J Thromb Haemost 90(3):446–455
50. Prandoni P, Falanga A, Piccioli A (2005) Cancer and venous thromboembolism. Lancet Oncol 6(6):401–410
51. Bottaro FJ, Elizondo MC, Doti C, Bruetman JE, Perez Moreno PD, Bullorsky EO, Ceresetto JM (2008) Efficacy of extended thrombo-prophylaxis in major abdominal surgery: what does the evidence show? A meta-analysis. Thromb Haemost. https://doi.org/10.1160/th07-12-0759
52. Kakkar VV, Balibrea JL, Martinez-Gonzalez J, Prandoni P (2010) Extended prophylaxis with bemiparin for the prevention of venous thromboembolism after abdominal or pelvic surgery for cancer: the CANBESURE randomized study. J Thromb Haemost. https://doi.org/10.1111/j.1538-7836.2010.03892.x
53. Clavijo-Alvarez JA, Pannucci CJ, Oppenheimer AJ, Wilkins EG, Rubin JP (2011) Prevention of venous thromboembolism in body contouring surgery: a national survey of 596 ASPS surgeons. Ann Plast Surg. https://doi.org/10.1097/SAP.0b013e3181e35c64
54. Nielsen LJ, Matzen SH (2017) Venous thromboembolism prophylaxis in plastic surgery: a survey of the practice in Denmark. J Plast Surg Hand Surg. https://doi.org/10.1080/2000656X.2016.1195745