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Original Article
Clinical Investigation

Can trajectory nor-epinephrine infiltration reduce blood loss during percutaneous nephrolithotomy? A double-blinded randomized controlled trial

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Abbreviations & Acronyms
AE = adverse event
CBC = complete blood count
EBL = estimated blood loss
Hct = hematocrit
IQR = interquartile range
NCCT = non-contrast computerized tomography
NE-PCNL = norepinephrine percutaneous nephrolithotomy
NT = nephrostomy tube
OT = operative time
POD = postoperative day
S.C. = serum creatinine
SFR = stone-free rate
S-PCNL = saline-percutaneous nephrolithotomy
US = ultrasound

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Purpose: To determine the efficacy and safety of trajectory infiltration with 1:150 000 Norepinephrine (NE) in reducing blood loss during percutaneous nephrolithotomy (PCNL).
Materials and methods: This is a prospective randomized double-blinded placebo-controlled trial. In all, 140 consecutive patients underwent PCNL for the management of large renal calculi. They were randomly assigned (1:1) to one of either study groups, the NE-PCNL group (70 patients whose PCNL-trajectory was infiltrated by NE) or the Placebo group (saline PCNL) (70 patients whose PCNL tracts were infiltrated by normal saline). Procedure-related blood loss (the primary outcome) was assessed and statistically analyzed. Also, all other procedure-related events and complications were recorded and compared.
Results: The median blood loss was 378 ml (IQR: 252–504) in the NE-PCNL group versus 592 ml (IQR: 378–756) in the S-PCNL group ($p < 0.0001$). In addition, Hemoglobin and Hematocrit deficits were lower in NE-PCNL ($p < 0.05$). Patients who were randomized to the NE-PCNL group had a higher immediate stone-free rate (SFR) (80%) compared with those of the S-PCNL group (70%) ($p = 0.034$). However, no statistical differences were found in the final SFR. The reported overall complications between the 2 groups were similar ($p > 0.05$). Indeed, bleeding-related complications were 1 (1.4%) versus 10 (14.3%) for NE-PCNL and S-PCNL, respectively ($p = 0.009$).
Conclusions: Trajectory infiltration of PCNL tracts by NE was found to be effective and safe in mitigation of PCNL-related blood loss. This step is a timeless and cost-effective as NE is readily available in surgical theaters and of very low cost.

Key words: blood loss, norepinephrine, PCNL, renal stones, stone free rate.

INTRODUCTION

Nephrolithiasis is a common health problem that affects approximately 1%–15% of the general population globally.[1] In the United States, about 11% of men and 7% of women report nephrolithiasis at least once during their lifetime. Indeed, this incidence is increasing over time.[2]

Nowadays, there is a consensus that percutaneous nephrolithotomy (PCNL) is the first-line monotherapy for the management of large (>20 mm), and/or complex renal stones.[3,4]

Despite PCNL having the highest stone-free rate (SFR) compared to other treatment modalities, it has considerable adverse events (AEs). One of the most common and dreadful AEs is bleeding which may necessitate; quitting the procedure, blood transfusion (with its morbidities), clot retention, and/or even angioembolization.[5]

In an attempt to prevent or lessen perioperative hemorrhage; many endourologists opted to minimize tract size by mini-PCNL[6] or administer antifibrinolytic medication such as tranexamic acid either parentally or as an add-on to irrigates.[7,8]

Norepinephrine (NE) is a potent vasoconstrictor that has been used as a hemostatic agent to reduce perioperative bleeding. Also, it has a procoagulant activity that increases fibrinogen

release, fibrinogen receptor activation, and activation of other coagulation factors. In addition, NE promotes thrombocytopoiesis, splenic contraction with a subsequent squeeze of more platelets into the circulation, and platelets activation, aggregation, and stabilization, besides its anti-inflammatory action.[9–11]

Although NE is frequently used to reduce peri-operative hemorrhage during different surgical procedures, yet; to our knowledge its use during PCNL has never been studied. We hypothesized that NE injection in the PCNL trajectory reduces surgical blood loss. Thus, we designed this prospective randomized placebo-controlled clinical trial to determine the efficacy and safety of trajectory infiltration with 1:150 000 NE in reducing blood loss during PCNL.

PATIENTS AND METHODS

Study populations

The study was conducted at Benha University Hospital which is a tertiary referral high-volume central hospital. The Local Research Ethics Committee (REC-FOMBU) approved the trial protocol, and it was registered on clinicalTrials.gov (NCT05035303). The trial followed Good Clinical Practice according to the declaration of Helsinki. Patients' recruitment was started in March 2020 through January 2022.

The present study included 140 consecutive patients eligible for PCNL (adult patients ≥18 years, stone/s diameter of at least 2 cm and American Society of Anesthesiology (ASA) score ≤ 3). Patients who had at least one of the following criteria were excluded; serum creatinine (S.C) > 1.5 mg/dl, coagulopathy, renal anomalies/transplanted kidney, or active urinary infection.

Preoperative evaluation

The preoperative evaluation included detailed medical & surgical history, physical examination, laboratory investigations including complete blood count (CBC), S.C, urine analysis culture and sensitivity (when indicated), coagulation profile, and radiological investigations (abdominal-pelvic ultrasound [US], kidney, ureter, and bladder radiography, and low dose non-contrast computerized tomography [NCCT]).

Sample size and randomization

Based on estimated blood loss (EBL) during PCNL which is the primary outcome of this study. As there are no previous reports about the role of NE during PCNL, we assumed that PCNL tract infiltration with NE may decrease EBL by >20% more than placebo (saline). The sample size was calculated with G*Power 3.1 (Heinrich-Heine) which was set as follows; allocation ratio (N2/N1) was 1, medium effect size (0.5), 1 — b err prob was 0.8, a err prob = 0.05, 95% confidence interval, and two tails *t*-test. The calculated minimum required sample size was 64 subjects per each study group. In anticipation of the possible attrition or drop-outs, the number of enrolled patients was raised to 70 subjects per each study group.

After patients' counseling, they signed well-informed written consents then they were randomly allocated into one of the following groups:

Group I: Seventy patients underwent PCNL after tract infiltration with 20 ml as an average (1:150 000) NE (NE-PCNL).
Group II: Seventy patients underwent PCNL after tract infiltration with an average of 20 ml of normal (0.9%) saline (S-PCNL).

A stratified block randomization method was employed, each block included 4 patients. The balance between both groups was kept by stratification and allocation of patients in each group according to their Guy's stone score as follows:

- Grade I: Patients with a solitary stone in the pelvis, lower, or middle calyx with simple anatomy (56 cases).
- Grade II: Patients with a solitary stone in the upper pole or multiple stones with simple anatomy, or a solitary stone with abnormal anatomy (44 cases).
- Grade III: Patients with multiple stones and abnormal anatomy or partial staghorn stone (28 cases)
- Grade IV: Patients with staghorn stone (12 cases)

The study participants, anesthesiologists, and outcomes assessors (e.g., radiology and laboratory professionals) unwitnessed the intervention assignment. Randomization, masking, and preparation of the injection fluid (saline/NE) were carried out by a third party who was blinded to the procedure and the surgeons were blinded to the agent used for tract(s) infiltration.

Surgical procedures

All patients received an empirical prophylactic antibiotic (ceftriaxone 1 g). If there was a positive urine culture, then an antibiotic was given pre-operatively for 3 days based on the antibiogram. All procedures were performed under general anesthesia, Surgeries were performed by two experienced endourologists (W.E., A.E.).

Patients of both groups were positioned either supine or prone according to surgeon predilection. PCNL was performed according to our previously mentioned protocol[12] with some modifications; firstly, under fluoroscopy and/or US guidance, all the primary tracts were dilated to 30F (conventional PCNL using a 26-F nephroscope [Karl Storz]). If secondary tracts were needed (in cases of multi-tracks) then, they were dilated to 15 F and a 12 F mini-nephroscope (RZ Medizintechnik GmbH) was utilized. The stones' disintegration was accomplished by a pneumatic lithotripter (Lithoclast Richard Wolf GmbH). Secondly, after insertion of the puncture needle into the desired calyx, thrusting guidewire, and before tract dilatation, a 22-gauge Chiba needle was introduced alongside the puncture needle to the subcapsular level provided that the targeted calyx was not reached. The tract was infiltrated by approximately 20 ml of either 1:150 000 NE or normal saline accordingly (about 150 ml from each agent was freshly prepared in a separate sterile container. And in the case of multiple tracts, then every tract was

infiltrated separately by the same agent) while the Chiba needle was withdrawn until subcutaneous level. Lastly, the placement of the nephrostomy tube (NT) at the end of the procedure was decided "when appropriate" according to intra-operative incidents. Some of the NE-PCNL steps are elucidated in Figure 1.

The resultant wash was thoroughly and carefully collected in a heparinized container (1000 units of heparin per container) at the conclusion of the procedure for an accurate determination of intra-operative blood loss as described by Bansal & Arora.[7] Briefly, for CBC analysis, about 2 ml of collected wash was transmitted to a K3 EDTA-containing bottle and mixed well by gentle inversion; the resultant value of Hb was multiplied by the collected irrigation volume and then divided by the pre-operative Hb level to calculate the total EBL. An automated Hematology Analyzer Sysmex KX-21N (Sysmex Corporation) was used for the measurement of all Hb, and Hematocrit (Hct) values.

Postoperative management and outcomes and measures

The primary endpoint of the present study is the total EBL. For calculation of EBL, Hb, and Hct deficits were measured Hb and Hct values were measured within 24 h before (Baseline values), and 72 h postoperatively. However, in cases whereas blood transfusion is required (in symptomatic [hypotensive] cases with Hb level ≤ 10 mg/dl not responding to intravenous fluids, but not in haemodynamically stable patients until Hb ≤7 mg/dl), Hb and Hct values were measured immediately before blood transfusion, for estimation of EBL, Hb, and Hct deficits. The secondary outcomes were operative time (OT), tubeless procedures. Patients were discharged after catheter removal and a successful voiding trial on the morning of the postoperative day 1 (POD). However, if NT was placed, then a nephrostogram was done before its removal to assure ureteral patency otherwise, the nephrostogram was

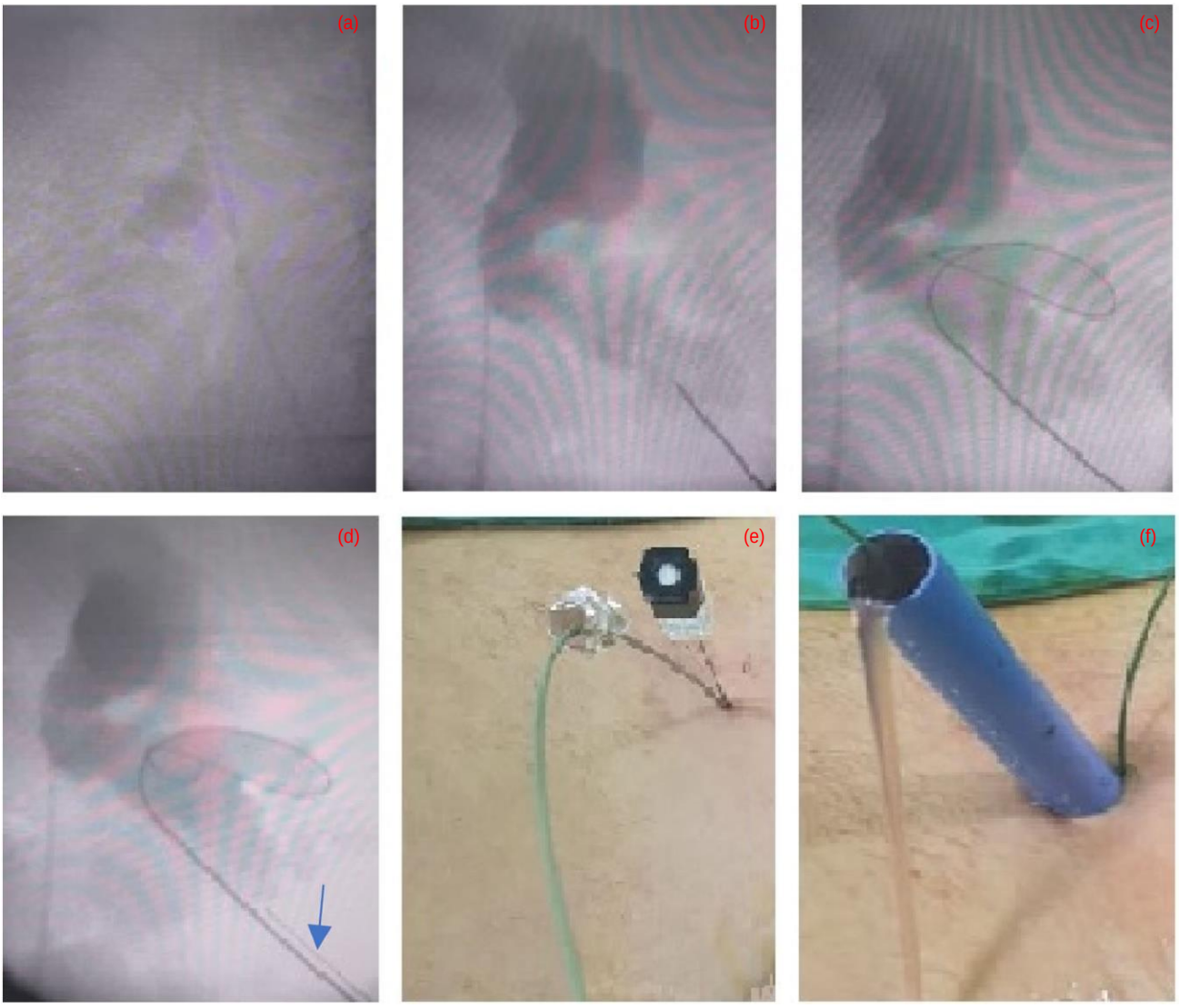

FIGURE 1 Some steps of nor-epinephrine percutaneous nephrolithotomy.

repeated (in obstructed cases) on POD 2, or a second look PCNL was planned, and after ruling out major hemorrhage or leakage. The hospital stay (defined as the number of days that the patient spends in the hospital) was calculated from the day of the surgery until discharge. AEs were reported according to the modified Clavien-Dindo classification.

The primary and final SFR was doubly assessed by a radiologist and urologist who were blinded to both the procedure and randomization based on the findings of low dose NCCT on the day after surgery and at 3 months later, respectively.

The determination of performing an auxiliary or additional maneuver based on the residual fragment(s) presence as well as their number, location, and accessibility as indicated in the first postoperative evaluation.

Statistical analysis

Quantitative data were given as a median and interquartile range (IQR) and tested for normality by the Kolmogorov–Smirnov test. The independent Student's *t*-test or Mann–Whitney *U* test was used for statistical analysis of these data as appropriate. Categorical data were presented as absolute and relative frequencies comparisons of these data were analyzed by v^2 or Fisher's exact tests when appropriate. All statistical analyses were conducted by SPSS ver26 (IBM). The significance levels were set at 0.05.

RESULTS

In this study, 175 patients were initially enrolled, out of them, 141 patients were allocated into 2 groups. Utterly; 70 patients per each group were included in the final statistical analysis (Figure 2).

As shown in Table 1, preoperative descriptive statistics revealed that there were no significant statistical differences in baseline patients' characteristics including age, sex, body mass index, comorbidities, degree of hydronephrosis, S.C, Hb, Hct, and stone characteristics (site, size, number, and location) between NE-PCNL and S-PCNL groups ($p > 0.05$).

The peri-operative findings are indicated in Table 2. The average Hb drop was 1.2 versus 1.5 ($p = 0.002$) in the NE-PCNL and the S-PCNL groups, respectively. While EBL in the NE-PCNL group (378 [252–504]) was significantly lower as compared to the corresponding value in S-PCNL (592 [37

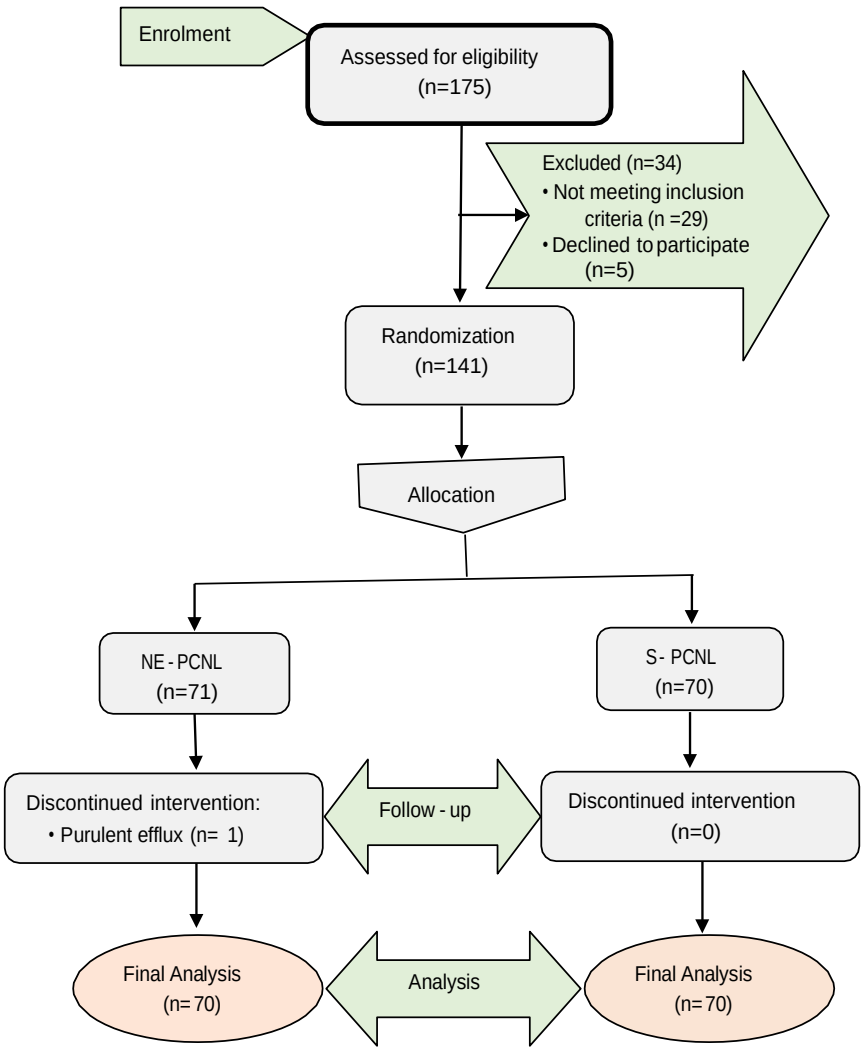

FIGURE 2 Flow diagram illustrating the study design.

TABLE 1 Descriptive preoperative patients' characteristics

Parameters	NE-PCNL (n = 70)	S-PCNL (n = 70)	p value
Age, years; median (IQR)	52 (43–64)	59 (47–67)	0.097
Sex (male/female)	49/21	52/18	0.572
Laterality (Rt/Lt)	47/23	46/24	0.858
Body mass index kg/m^2, median (IQR)	27.7 (25.4–31)	29 (27–30.3)	0.203
Comorbidities, n (%)	29 (41)	33 (47)	0.527
Hypertension	12 (17)	12 (17)	
Diabetes mellitus	7 (10)	13 (18.6)	
Both (1 and 2)	10 (14)	8 (11)	
Hydronephrosis, n (%)			0.253
None	16 (22.8)	15 (21.4)	
Mild	23 (32.9)	24 (34.2)	
Moderate	25 (35.7)	30 (43)	
Severe	6 (8.5)	1 (1.4)	
Serum creatinine (mg/dl)	1.1 (1–1.2)	1.1 (1–1.3)	0.458
Hemoglobin (g/dl, mean SD)	14.6 1.5	14.2 1.5	0.134
Hematocrit (%; median (IQR))	39 (37–41)	39 (37–41)	0.710
Stone size, mm; median (IQR)	33.5 (26–44)	32 (28–45)	0.630
Stone density, HU, median (IQR)	773 (586–1068)	775 (578–1078)	0.750
Stone type, n (%)			0.914
Single	33 (47)	32 (46)	
Multiple	24 (34)	23 (33)	
Staghorn	13 (19)	15 (21)	

Abbreviations: IQR, interquartile range; NE-PCNL, norepinephrine percutaneous nephrolithotomy; S-PCNL, saline percutaneous nephrolithotomy.

TABLE 2 Operative and postoperative parameters' comparisons

	NE-PCNL (n = 70)	S-PCNL (n = 70)	p value
Targeted calyx, N (%)			0.157
• Lower	55 (79)	52 (74)	
• Middle	22 (31)	30 (43)	
• Upper	10 (14)	12 (17)	
Patient's position, N (%)			0.384
• Supine	41 (59)	46 (66)	
• Prone	29 (41)	24 (34)	
Working tracts, n; (%)			0.288
• Single	55 (79)	49 (70)	
• Multiple	15 (21)	21 (30)	
Operative time, min; median (IQR)	60 (47–90)	81 (55–98)	0.008*
Irrigation volume, L; median (IQR)	7 (6–11)	10 (8–13)	0.002*
Tubeless/tube, n; (%)	39(56) / 31 (44)	25(36) / 45 (64)	0.018*
Hemoglobin drop (g/dl, median (IQR))	1.2 (0.8–1.7)	1.5 (1.2–2.3)	<0.001*
Hematocrit, %; median (IQR)	36 (34–38)	34 (32–35)	<0.001*
Estimated blood loss, ml; median (IQR)	378 (252–504)	592 (378–756)	<0.001*
Serum creatinine, mg/dl; median (IQR)	1.2 (1–1.5)	1.3 (1–1.5)	0.193
Hospital stay; days, median (IQR)	2 (1–2)	2 (1–3)	0.013*
1ry SFS, N (%)	56 (80)	49 (69)	0.034*
• No residual fragments	36 (51)	21 (30)	
• Insignificant fragments	20 (29)	27 (39)	
• Significant fragments	14 (20)	22 (31)	
Auxiliary procedures, N (%)	10 (14)	19 (27)	0.297
• 2nd look PCNL	2 (2.9)	5 (7)	
• ESWL	6 (8.6)	11 (16)	
• Uretroscopy	2 (2.9)	3 (4)	
Final SFR, N (%)	67 (95.7)	65 (92.9)	0.466

Abbreviations: IQR, interquartile range; NE-PCNL, norepinephrine percutaneous nephrolithotomy; S-PCNL, saline percutaneous nephrolithotomy; SFR, stone-free rate; ESWL, extracorporeal shock-wave lithotripsy. *p < 0.05.

–756]), (p < 0.001). In addition, in S-PCNL group, the OT was longer, the irrigation volume was larger, and the length of hospital stay was longer as compared to the corresponding values in NE-PCNL group (p < 0.05). The tubeless procedure rate was 56% versus 36% in the NE-PCNL group and the S-PCNL group, respectively (p = 0.018) The placement of NT was indicated in cases of significant bleeding, residual stone, major injury of the collecting system, infection stones, and if multi-tracts have been undertaken. A Double J stent was inserted if there was a major laceration of pelvicalyceal system, oedema and/or injury of pelviureteral junction or ureter and it was removed 2 weeks later as an outpatient procedure. Also, the primary SFR (after a single session PCNL procedure) was higher in patients in the NE-PCNL group (80%) as compared to the SFR rate in the S-PCNL group (69%) (p = 0.034).

There were no statistically significant differences between both study groups regarding the number of working tracts, postoperative S.C levels, auxiliary procedures, or final SFR (p > 0.05).

The overall complication rate was similar between the two study groups. AEs were reported in 15 (21%) and 21 (30%) patients in the NE-PCNL group and the S-PCNL group, respectively (p = 0.246). Individual complications are mentioned in number and frequency in Table 3. Interestingly, one patient in the NE-PCNL group complained of tachypnea, dyspnea, chest pain, and tachycardia 1 day after discharge. On reviewing his past history, it was found that he had a previous attack of subsegmental pulmonary embolism 1 year earlier. The patient was admitted to the intensive care unit as he was suspected to have an impending pulmonary embolism (grade IV according to modified Clavien–Dindo classification) depicted by proper clinical and investigational findings. The patient received intensive proper management for 2 days, and then he was discharged uneventfully.

DISCUSSION

Percutaneous nephrolithotomy is the treatment of choice for bulky renal stones. The benchmark step of this procedure to be reproducible is the creation of a suitable tract that is associated with a great risk of bleeding.[13] The kidney is a highly vascular organ and the renal blood flow is about 1200 ml/min (~400 ml/100 g renal-tissue/min) which composes about ¼ of cardiac output.[14]

Since the inception of the PCNL as an option for renal stones management, the procedure is continuously modified mainly to reduce access-associated AEs and bleeding. Such

TABLE 3 30 days Postoperative adverse events according to modified Clavien classification of complications, *N* (%)[a]

Complication	NE-PCNL (*n* = 70)	S-PCNL (*n* = 70)	MC grade	*p* value
Overall	15 (21.4)	21 (30)	I:IV	0.246[b]
Tube displacement	1/31 (3)	1/45 (2)	I	0.790[c]
Postoperative fever >38°	4 (5.7)	10 (14.3)	I	0.157
Transient elevation of serum creatinine	3 (4.3)	2 (2.9)	I	1
Bleeding required transfusion	1(1.4)	3 (4.3)	II	0.620
Clot retention	0 (0)	4 (5.7)	II	0.120
Urinary tract infection	12 (17)	16 (23)	II	0.527
Double-J stenting due to persistence leakage >48 h	2 (2.9)	2 (2.9)	IIIA	1
bleeding required quitting the operation	0 (0)	3 (4.3)	IIIB	0.245
Pleural effusion	2 (2.9)	2 (2.9)	IIIB	1
Pulmonary embolism	1(1.4)	0 (0)	IV	1
The sum of individual complications	26 (37)	43 (61)	I–IV	0.002

[a]Some patients had simultaneous complications. And Fisher's exact test was used (all *p* values except[b]). [b]Chi-Square test. [c]Tubeless procedures were excluded.

modifications include miniaturization PCNL, reduction in the use of multi-tracts via incorporation of Endoscopic combined intrarenal surgery, position modifications (supine positions), utilization of power Doppler ultrasound guidance, administration of antifibrinolytics such as tranexamic acid, and/or sealing the tract with hemostatic agents as an exiting trategy.[15–17] Several risk factors or predictors of bleeding complications during PCNL such as OT, stone burden, case- load, tract dilatation technique, and sheath size had been reported.[18] Besides, undue torquing and over-manipulation of the nephroscope and the sheath, non-papillary puncture of the collecting system, and medial dilation had been reported. So, to prevent this dreadful complication, several tips were described such as; avoidance of medial dilatation and excessive intrarenal manipulations, and use of flexible scopes to reach inaccessible stones, targeting the posterior lower calyx along its axis and avoiding accessing the upper pole as much as possible.[19,20] In addition, in clinical practice; several hemostatic agents are advocated to mitigate bleeding resulting from different surgical settings especially major ones such as Hemocoagulase Bothrops Atrox and tranexamic acid[21]

The use of NE to reduce hemorrhage during different surgical settings was common and well known. Yet, there was no consensus about the optimum dose and/or concentration of its use (concentration may range from 1:50 000 to 1:400 000). It can be infused locally, systematically or tamponade the operative bed with NE-soaked gauzes with no significant associated AEs.[9,11,22–24]

The objective of this study was to investigate the effect of infiltration of NE during PCNL in the mitigation of perioperative blood loss. Our results revealed that; there was a significant difference in EBL between the two study groups (378 [252–504] versus 592 [378–756]; $p > 0.001$) in favor of the NE-PCNL group. Not surprisingly, the Hb drop was lower in the NE-PCNL (1.2 g/dl [0.8–1.7]) than in the S-PCNL group (1.5 g/dl [1.2–2.3] $p = 0.002$). These findings are in line with the results of many previously published studies that investigated the effect of systemic and/or local administration of vasopressor agents (epinephrine/NE) on Blood Loss during major surgical procedures, such as Total hip or knee arthroplasty. These studies concluded that there was a clinically and statistically positive effect of these agents on the reduction of blood loss related to surgery. In addition, these hemostatic agents are physiologically Justified when mindfully used.[9,10,22,24,25] Another interesting study led by Wuethrich et al. deduced that continuous NE infusion reduces blood loss, blood transfusion rate, and the number of transfused units required per patient who underwent radical cystectomy.[26] Furthermore, in a recently published study that included 120 patients who were divided into 2 groups, El-Shaer and his colleagues found that, patients whose PCNL trajectory infiltrated by a mixture of local anesthesia contained NE had a lower Hb drop as compared to patients of the control group whom their PCNL trajectory was not infiltrated by NE.[27]

Regarding the secondary outcomes, the median OT was shorter in the NE-PCNL group than in the S-PCNL group (60 vs. 81 min, $p = 0.008$). Indeed, the decrease in the OT in the NE-PCNL group is in apparent contradiction with our previous study whereas we reported that there is no significant difference in OT between patients whose PCNL trajectory was infiltrated by NE or not.[27] This contradiction might be attributed to the differences in the stone characteristics between both studies. In addition, there was a statistically significant difference in the average volume of irrigation fluid used during the procedure between the 2 groups. Thus, in patients of the S-PCNL group, higher volumes of irrigation fluids ($p = 0.002$) were needed and at the end of the procedures, the surgeons' decision to place a NT was 44% versus 64% ($p = 0.018$) for NE-PCNL & S-PCNL groups, respectively. The plausible explanation for these results is that the hemostatic effect of NE infiltration on the operative field provides a much clearer vision. Thus, the time and irrigant volumes spent for acquiring a reasonably suitable visual field were saved. Also, NE infiltration resulted in a clear field at the conclusion of the procedure which is one of the pivotal determinant factors in the decision to place a NT or not.[28]

Interestingly, the results of the current study revealed that the primary SFR was higher in the NE-PCNL group (80%) as compared to the S-PCNL (69%) group ($p = 0.034$). In addition, the hospital stay was significantly shorter in NE-PCNL than in the control group ($p = 0.013$). However, the final SFR was similar between both groups. This finding might be attributed to the better operative field in the NE-PCNL group. In fact, the concept that the clear visibility of the operative field (minimal bleeding) improves the procedural short and long-term outcome has been previously discussed and elaborated by many authors.[29]

In a recently published Meta-Analysis, it has been stated that the intraoperative endoscopic view can be impaired by bleeding and prolonged OT, which in turn increases the risk of more bleeding during PCNL and vice versa. Moreover, clear endoscopic views are associated with less consumption

of irrigating fluid, intraoperative injuries, and improved stone clearance rates as well.[30]

In the present study, the overall reported complications were similar between the 2 study groups as 15 patients (21%) reported at least 1 AE in the NE-PCNL arm versus 21 patients (30%) in the S-PCNL (p = 0.246). However, on the calculation of procedure-related AEs individually, it was found that there was a statistically significant (p = 0.002) difference between the 2 study groups (Table 3). Interestingly, on the computation of AEs related to perioperative bleeding (intraoperative bleeding crippled the procedure, clot retention, and transfusion), it was noted that there was a clinically and statistically significant difference between both groups (overall bleeding-related complications were 1 patient (1.4%) compared to 10 patients (14.3%) for NE-PCNL and S-PCNL respectively p = 0.009) as indicated in Table 3.

The safety of PCNL trajectory infiltration with NE is evident in the current study as none of the recruited patients developed any complication related to NE injection especially surgical site skin necrosis due to concern that NE could result in vasoconstriction which may lead to permanent skin loss. Furthermore, no clinically significant vital signs disturbances during intra-operative patients' monitoring were noted or recorded. This is in line with a previously reported finding by Pancaro et al. who concluded that none of their patients experienced short- or long-term AEs due to NE extravasation.[23]

One of the limitations of the present study is the relatively small sample size which impeded the estimation of the transfusion rate between both groups. So, a further study with larger sample size is needed to confirm our results and emphasize this clinically important point (transfusion rate). In conclusion: Norepinephrinization of the PCNL trajectory is helpful in the mitigation of peri-operative bleeding related to PCNL. This is a timeless, safe, and cost-effective step during PCNL as NE is readily available in all surgical suits and of a very low price. Besides, the reduction of bleeding resulted in a clearer visual field, lesser hospital stay, more ratio of tubeless procedures, and more primary stone clearance. Despite all of that, further studies are warranted to affirm these results.

AUTHOR CONTRIBUTIONS

Waleed El-Shaer: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; validation; visualization; writing – original draft; writing – review and editing. Mohamed Salah Haggag: Data curation; methodology; supervision; writing – review and editing. Alaa Elshaer: Conceptualization; investigation; software; supervision; writing – original draft. Islam Shaboob: Formal analysis; methodology; supervision; visualization. Wael Kandeel: Data curation; investigation; supervision; validation. Basheer Elmohamady: Formal analysis; funding acquisition; supervision; writing – review and editing. Dina Saad Abdelmotaleb: Formal analysis; methodology; supervision; validation. Sally Abdel-Lateef: Conceptualization; data curation; investigation; methodology; project administration; validation; writing – original draft; writing – review and editing.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

INFORMED CONSENT

Informed, written consent has been obtained.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

The study was registered on clinicalTrials.gov (NCT05035303).

ANIMAL STUDIES

N/A.

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