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Perioperative application of dexmedetomidine for postoperative systemic inflammatory response syndrome in patients undergoing percutaneous nephrolithotomy lithotripsy: results of a randomised controlled trial

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ABSTRACT

Objective Our previous retrospective study demonstrated that perioperative dexmedetomidine (Dex) administration was associated with low systemic inflammatory response syndrome (SIRS) incidence. The present study was designed to investigate whether perioperative administration of Dex decreases the incidence of postpercutaneous nephrolithotomy lithotripsy (PCNL) SIRS in patients who undergo PCNL.

Design A randomised controlled trial was designed.

Participants A total of 190 patients were randomly assigned to receive Dex (DEX group, n=95) or saline control (CON group, n=95) and completed the study. In the DEX group, Dex was loaded (1 µg/kg) before anaesthesia induction and was infused (0.5 µg/kg/h) during surgery.

Outcomes The incidences of postoperative SIRS were recorded. Serum interleukin-6 (IL-6) and tumour necrosis factor α(TNF-α) were measured.

Results The incidence rates of SIRS were significantly lower in the DEX group than in the CON group (35.8% vs 50.5%, p=0.04). No patients developed sepsis in either group. These results might be attributed to inhibition of inflammatory responses and the resulting lower serum levels of IL-6 and TNF-α, caused by Dex administration. However, compared with the CON group, the lower incidence rate of SIRS in the DEX group did not result in better outcomes, such as shorter postoperative hospitalisation stays and lower costs.

Conclusion The present study showed that Dex administration during PCNL might be beneficial for decreasing the incidence of SIRS through inhibiting the release of inflammatory mediators, but not clinical consequences such as postoperative hospitalisation duration and costs. Further effects of Dex administration on SIRS in patients who are scheduled for PCNL should be explored in future studies.

Trial registration number ChiCTR-ICR-15006167.

Strengths and limitations of this study

- ► Dexmedetomidine (Dex) administration during percutaneous nephrolithotomy lithotripsy (PCNL) decreased the incidence of postoperative systemic inflammatory response syndrome (SIRS) incidence.
- ► Low SIRS incidence did not result in better outcomes, such as shorter postoperative hospitalisation stays and lower costs.
- ► The study was a single-centre clinical trial and only explored Dex on post-PCNL SIRS in patients with American Society of Anesthesiologists class I and II.

INTRODUCTION

As a minimally invasive procedure, percutaneous nephrolithotomy lithotripsy (PCNL) has been recommended as an ideal choice for patients suffering from intrarenal calculi, especially those greater than 20 mm and staghorn calculi.[1 2] However, the risk of complications after PCNL was more than 20%.[3] Postoperative complications range from fever and systemic inflammatory response syndrome (SIRS) to severe sepsis.[4 5] Varying incidence rates of SIRS have been reported and the rates could be as high as 40%.[6–8] Due to the excessive inflammatory response, post-PCNL SIRS prolongs hospital stays, adds to healthcare costs and even increases mortality.[3 9] Thus, it is valuable to explore procedures that could minimise infection-related complications, including SIRS and sepsis.

Dexmedetomidine (Dex), a highly selective α2 receptor agonist, has been widely

used as a sedative, anaesthesia adjunct and sympatholytic.[10 11] Furthermore, a previous study has demonstrated that perioperative Dex administration might inhibit inflammatory responses during cardiopulmonary bypass.[12] Perioperative adjunctive administration of Dex during general anaesthesia substantially decreases the expression of serum inflammatory markers.[13] In rats, Dex could inhibit the production of proinflammatory cytokines.[14 15] Dex even prevented the development of cognitive dysfunction following systemic inflammation in aged rats.[16] Our previous retrospective study demonstrated that perioperative Dex administration is associated with low SIRS incidence.[17] Based on its effect on inflammatory responses and on the results of aforementioned studies, it is reasonable to assume that perioperative administration of Dex could protect patients who undergo PCNL from postoperative SIRS. Therefore, the current clinical trial was designed to investigate whether perioperative administration of Dex decreases the incidence of post-PCNL SIRS in patients who undergo PCNL.

MATERIALS AND METHODS

Study subjects

This randomised, double-blinded, prospective parallel study was performed in accordance with the Declaration of Helsinki . This manuscript adhered to the applicable Consolidated Standards of Reporting Trials 2010 checklist.

All patients who were scheduled for elective PCNL from 1 March 2015 after registering at the hospital were considered for inclusion. The inclusion criteria were: (1) age of 20–75 years, (2) American Society of Anesthesiologists (ASA) Physical Status I/II, (3) absence of clinical infections or positive urine culture and (4) obtained informed written consent. Patients who met any of the following criteria would be excluded: (1) recent history of nephrostomy or ureteral stent implantation; (2) pre-existing heart disorders, including sick sinus syndrome, atrioventricular block or sinus bradycardia; (3) long-term use of sedative drugs; (4) neurological or psychiatric illness; (5) history of tumours, blood disease or chemotherapy; (6) fever within one week or (7) undergoing another surgery simultaneously. Patients who were transferred to open surgery during the operation and those who failed to be followed up were excluded from the final analysis.

Patients were randomly assigned to receive Dex (DEX group) or saline (control (CON) group), according to computer-generated random numbers. This procedure was conducted by SZ. Block randomisation was not used. The random number was sealed in an envelope until the enrolled patient was in the operation room. To maintain blinding, the anaesthetist who prepared and administered the anaesthesia helped collect data, but was not involved in management or assessments. The treatment would be revealed when emergencies occurred, such as serious bradycardia and hypotension which was not sensitive to drug. All patients were blind to the intervention. Patients received standardised care during the perioperative period.

Sample size

This study was a randomised clinical trial with two parallel groups. The main outcomes were the incidence of SIRS. According to previous reports, the SIRS incidence varied and could be as high as more than 40%.[18 19] Our previous retrospective study revealed that SIRS incidence was around 35% without administration of Dex (CON group) after PCNL.[17 20] It was assumed that Dex would halve the SIRS incidence (from 35% to 17.5%). The following formula for calculating sample sizes was adopted:

$$n = \frac{\left(Z\alpha\sqrt{2\bar{p}\bar{q}} + Z\beta\sqrt{p0q0 + p1q1}\right)^2}{(p1 - p0)^2}$$

Ninety participants were required in each group with a power of 80% and a two-tailed 0.05 was considered as statistically significant. Considering that there may be about 10% of patients who drop out during the research, 99 patients were enrolled in each group and the total number of patients was 198. The inclusion and exclusion procedures are shown in figure 1.

Procedures

In the DEX group, Dex was loaded (1 µg/kg) for 15 min before anaesthesia induction and was infused (0.5 µg/kg/hour) during surgery according to the drug instructions and previous studies.[21] The patients in the CON group were administered the same volume of saline as that of Dex administered in the DEX group. Both the Dex and saline were prepared in a 50 mL syringe, and both had the same appearance. Anaesthesia was induced with intravenous midazolam (0.035 mg/kg), fentanyl (3 µg/kg), propofol (1.5–2 mg/kg) and cisatracurium (0.2 mg/kg) and maintained with end-tidal sevoflurane (2%–2.5%). Ventilation was controlled with 8–10 mL/kg tidal volume with end-tidal CO_2 of 35–45 mm Hg. Vasoactive drugs including dopamine, nitroglycerine and phenylephrine were used to maintain blood pressure in the normal range according to haemodynamic responses when necessary, and atropine was used if heart rates were less than 50 beats/min. Thirty minutes before the end of surgery, patients were intravenously infused with flurbiprofen axetil (1 mg/kg) as an analgesic and tropisetron (5 mg) to prevent vomiting.

One anaesthetist recorded the data in case report form. The patients monitor screen could record the haemodynamics data. Another anaesthetist would check the form according to the monitor record and anaesthesia record.

All patients received standardised antibiotics. The patients received single doses of broad spectrum antibiotics intravenously at the time of anaesthesia induction until nephrostomy tube removal.

The outcomes

The primary outcome was the incidence of postoperative SIRS. The other outcomes included residual stones, severe haemorrhage, renal arterial embolisation, hypotension, bradycardia and other complications.

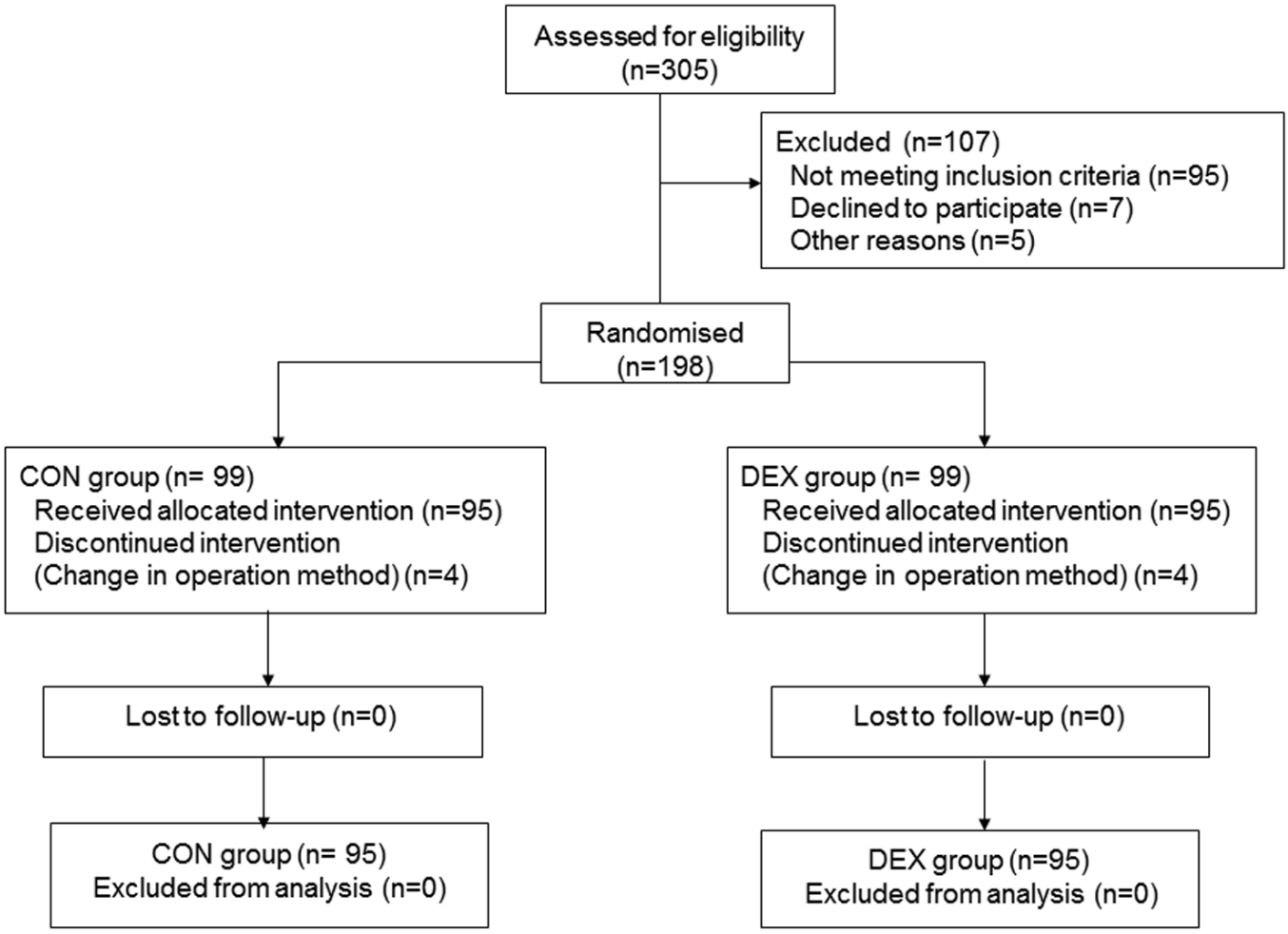


Figure 1 The flow chart of inclusion and exclusion. CON, control; DEX, dexmedetomidine.

Postoperative-hospitalisation stay and hospitalisation costs were also recorded.

Follow-up

Side effects potentially related to Dex, such as bradycardia and hypotension, were recorded. Bradycardia was defined as a heart rate less than 50 beats/min, and hypotension was defined as the mean arterial pressure being less than 30% from baseline or a systolic blood pressure decrease of less than 90 mm Hg for 3 min.[22]

Follow-up evaluations were performed on postoperative day 1–3 (24, 48 and 72 hours after surgery). Venous blood (5 mL) was collected before the surgery (T0), at the end of the surgery (T1) and at 24 (T2) and 48 hours (T3) after surgery. Samples were centrifuged at 2000×g for 10 min in a refrigerated centrifuge. Thereafter, the serum was stored at −80°C for future measurement of interleukin-6 (IL-6) and tumour necrosis factor α (TNF-α).

SIRS was diagnosed when a patient met two of the following four criteria[23]: (1) body temperature >38°C or <36°C, (2) heart rate >90 beats/min, (3) respiratory rate >20 breaths/min or arterial carbon dioxide tension <32 mm Hg and (4) leucocyte count >12× 10^9/L or <4 × 10^9/L . The incidence of postoperative SIRS three days postoperative was recorded in the present study.

Statistical analysis

Quantitative data were expressed as mean±SD, and qualitative data and ordinal data as absolute frequencies. The one-sample Kolmogorov-Smirnov test was used to test the normality of quantitative data. The Student's t-test or non-parametric test was used to analyse quantitative variables according to the distribution of these data. The χ^2 test or Fisher's exact probability was used to compare the difference between qualitative data. SPSS V.19.0 software was used to perform statistical analyses. Differences were considered significant when the two-tailed p values were <0.05.

Patient and public involvement

No patients or public members were involved in the development of the research question or recruitment or outcome measures nor the design of the study. There are no plans to disseminate the results of the research to study participants.

Table 1 Clinical characteristics

Patient characteristic	Dexmedetomidine group (n=95)	Control group (n=95)	P values
Age (year)	49.29±11.25	49.37±11.60	0.965
Gender (F)	53 (55.8%)	52 (54.7%)	0.884
Body mass index (kg/m^2)	22.99±3.23	23.37±3.26	0.424
American Society of Anesthesiologists (II)	51 (53.7%)	60 (63.2%)	0.185
Hypertension	18 (18.9%)	18 (18.9%)	1.000
Diabetes	5 (5.3%)	9 (9.5%)	0.267
White cell count (×10^9/L)	7.11±2.05	7.25±2.34	0.670
Haemoglobin (g/dL)	13.54± 1.87	13.50± 2.08	0.917
Urea nitrogen (mmol/L)	5.58±2.53	5.84±2.14	0.457
Serum creatinine (μmol/L)	90.30±39.08	86.74±30.22	0.484
Stone size (≥20 mm)	59 (63.4%)	59 (63.4%)	1.000
Stone (multiple)	58 (61.1%)	51 (53.7%)	0.304
Maximum diameter of stone (mm)	21.21±9.84	23.75±14.33	0.154
Staghorn stone	22 (23.3%)	28 (29.5%)	0.323
Hydronephrosis	82 (86.3%)	82 (86.3%)	1.000
Urinary white cell count (/uL)	473.81±167.13	676.18±238.57	0.486
Operation time ≥2 hours	11 (11.6%)	11 (11.6%)	1.000
No of involved tract (single)	82 (86.3%)	84 (88.4%)	0.662
Tract size			0.279
18–20 (F)	14 (14.7%)	6 (6.3%)	
21–24 (F)	9 (9.5%)	12 (12.6%)	
25–30 (F)	72 (75.8%)	77 (81.1%)	
Blood transfusion	2 (2.1%)	1 (1.1%)	0.561

RESULTS

A total of 198 patients were randomly assigned to the DEX group or CON group. Eight patients were excluded for being transferred to open surgery. A total of 190 patients completed the study and were included in the final analyses (figure 1). Demographics and surgical aspects did not differ significantly between the two groups (table 1).

Outcomes

The incidence rates of SIRS were significantly lower in the DEX group than in the CON group (35.8% vs 50.5%, p=0.04, table 2). No patients developed sepsis in either group.

There were three patients in the DEX group and one in the CON group that developed pneumonia. Three patients in each group were diagnosed with acute kidney injury (table 2).

Concerning the residual stones, the differences between the two groups were not statistically significant. Four patients in the DEX group and three in the CON group suffered severe haemorrhage, and six of them underwent renal arterial embolisation without differences between the two groups (table 2).

Postoperative TNF-α and IL-6 levels

Regarding the serum TNF-α levels, the expression showed a significant increase from initial surgery (T0) to 24 hours after surgery (T1) in the CON group (21.58±9.20 ng/L vs 13.49±7.11 ng/L, p=0.002), but not in the DEX group. The differences between the two groups at T1 were statistically significant (12.52±6.66 ng/L vs21.58±9.20 ng/L, p=0.001, figure 2).

IL-6 levels increased significantly from beginning of surgery (T0) to 48 hours after surgery (T2) in CONgroup (11.49±3.56 ng/L vs 17.46±9.36 ng/L for T0 vs. T1 and 11.49±3.56 ng/L vs 15.41±8.3 ng/L for T0 vs. T2, p=0.009 and p=0.002), while the statistically significant increase was only observed at T1 in the DEX group (11.39±3.69 ng/L vs 17.00±6.65 ng/L, p=0.049). Therefore, the DEX group had lower IL-6 levels, though the change was only statistically significant at T2 (7.30±1.70 ng/L vs 15.41±8.3 ng/L, p<0.001, figure 2).

Complications and prognosis

The DEX group had higher postoperative bradycardia rates than the CON group (41.1% vs 17.9%, p<0.001, table 2), though most of the bradycardia was transient. Eight patients in the DEX group and two in the CON

Table 2 Outcomes and complications

Variables	Dexmedetomidine group (n=95)	Control group (n=95)	P values
Systemic inflammatory response syndrome	34 (35.8%)	48 (50.5%)	0.040
T>38°C or <36°C	20 (21.1%)	19 (20%)	0.857
Heart rate >90 beats/min	23 (24.2%)	22 (23.2%)	0.865
Leucocyte count >12 × 10^9/L or <4 × 10^9/L	53 (55.8%)	41 (43.2%)	0.082
Respiratory rate >20 breaths/min	48 (50.5%)	44 (46.3%)	0.561
Hypotension	23 (24.2%)	17 (17.9%)	0.286
Bradycardia	39 (41.1%)	17 (17.9%)	<0.001
Atropine required	8 (8.4%)	2 (2.1%)	0.051
Residual stones	44 (46.3%)	47 (49.5%)	0.663
Severe haemorrhage	4 (4.2%)	3 (3.2%)	1.000
Renal arterial embolisation	4 (4.2%)	2 (2.1%)	0.407
Pneumonia	3 (3.2%)	1 (1.1%)	0.621
Acute kidney injury	3 (3.2%)	3 (3.2%)	1.000
Postoperative hospitalisation stays (days)	7.79±3.49	7.99±3.41	0.690
Hospitalisation expense (¥1000)	30.80±10.29	30.00±9.69	0.605

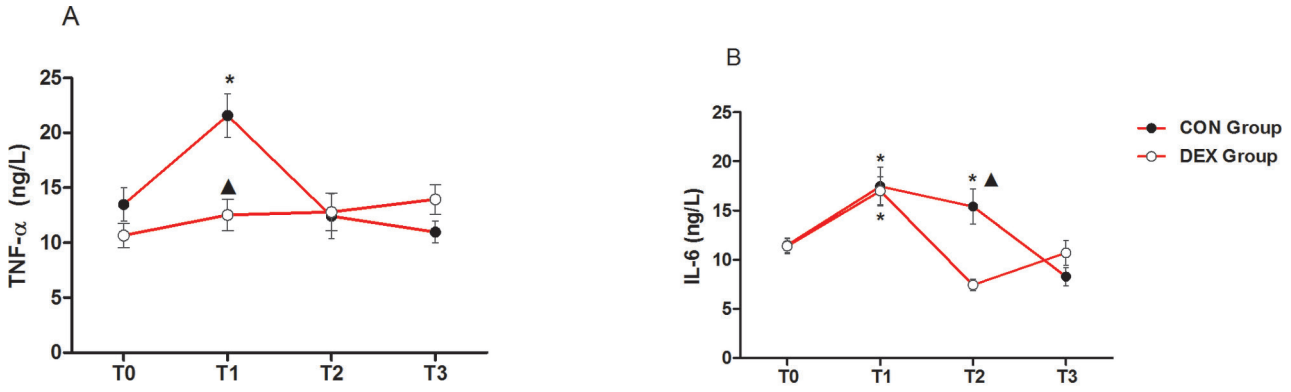
group needed atropine, and all of them were sensitive to atropine. No other serious complications occurred.

Regarding postoperative hospitalisation stays and costs, there were no significant differences between the two groups (table 2).

DISCUSSION

The present study demonstrated that perioperative application of Dex in patients who underwent PCNL could decrease the incidence rate of postoperative SIRS compared with saline administration. These results might be attributed to inhibition of inflammatory responses and the resulting lower serum levels of IL-6 and TNF-α, caused by Dex administration. However, compared with the CON group, the lower incidence rate of SIRS in the DEX group did not result in better outcomes, such as shorter postoperative hospitalisation stays and lower costs.

Because of high cure rates, low recurrence rates and low postoperative complications, PCNL has been recommended as a gold standard in the management of intrarenal calculi, especially for large and staghorn calculi.[24] However, postoperative PCNL complications could not



Data in figure are presented as mean ± standard deviation.

T0: preoperation; T1: postoperation; T2: 24 hours after operation; T3: 48 hours after operation

A: TNF-α, tumor necrosis factor alpha; B: IL-6, interleukin-6

*p<0.05 for T0 vs. T1; ▲p<0.05 for CON Group vs. DEX Group

Figure 2 The expression of TNF-α and IL-6. CON, control; DEX, dexmedetomidine.

be avoided until now. Among the complications, SIRS is one of the most dreadful, which might lead to deleterious prognosis including requiring intensive care and even mortality.[6 7] Several factors including female sex, old age, diabetes mellitus, composition of stones, degree of hydronephrosis and urine culture could predict incidence of SIRS or sepsis.[25 26] However, most of the factors, except urine culture, are difficult to control or the pertinent data are not available before surgery. Therefore, to decrease the incidence of SIRS, intraoperative intervention might be needed in addition to administration of empirical broad-spectrum antibiotics. The present study demonstrated that intraoperative application of Dex could lower postoperative SIRS incidence, which was consistent with the results of our previous retrospective study.[17]

Dex has been widely used as an anaesthetic adjuvant during surgery because of its ability to stabilise haemodynamics and improve stress responses.[27] Previous studies demonstrated that Dex administration could inhibit the release of inflammatory cytokines and reduce perioperative complications.[12 28] Furthermore, in vitro or in vivo studies, Dex could significantly suppress lipopolysaccharide-induced proinflammatory mediator production, including TNF-α, IL-6 and IL-8.[13–15 29] In line with these studies, the present study showed that Dex could alleviate the release of serum IL-6 and TNF-α.

SIRS represents a complex interplay of proinflammatory and anti-inflammatory reactions, which accompanies the excessive release of pro-inflammatory cytokines including TNF-α and IL-6.[30] IL-6 is a glycoprotein produced by various types of cells, such as mononuclear macrophages, and is believed to reflect inflammatory and oxidation conditions.[31] A study reported that the severity of SIRS is positively related with serum IL-6 levels and concluded that the concentration of IL-6 might be a sensitive index for the prediction of SIRS occurrence.[32] Like IL-6, TNF-α was also proved to be a sensitive factor in inducing and maintaining inflammatory responses.[33] Therefore, IL-6 and TNF-α play a crucial role in SIRS progression.[34] The present study found that, in comparison with saline, Dex administration perioperatively decreased postoperative IL-6 and TNF-α expression significantly, indicating that Dex might decrease the incidence of SIRS through inhibiting the release of inflammatory mediators. However, it should also be noted that TNF-α and IL-6 showed different time trends, which might be attributed to the small sample size in the present study. Therefore, further studies including cell and animal studies are needed to explore the underlying mechanisms of Dex.

However, in the present study, Dex could only reduce the incidence of SIRS, but not the consequential clinical outcomes including the incidence of sepsis, and postoperative hospitalisation stays and costs. It might be partly attributed to the SIRS criteria, which were found to be too sensitive and insufficiently specific to screen patients for identifying SIRS outside intensive care units (ICUs) in recent studies.[35 36] In line with a previous study, almost half of the patients in the present study developed SIRS.[35] However, no patients developed sepsis in either the DEX group or the CON group. During the procedure of the present study, the Third International Consensus Definitions for Sepsis and Septic Shock updated the definition of sepsis and introduced a new clinical score (quick Sequential Sepsis-related Organ Failure Assessment, qSOFA) to identify patients at risk of sepsis outside the ICU instead of SIRS.[37] Recent studies have demonstrated that qSOFA has greater accuracy than SIRS for predicting clinical outcomes.[36 38] Therefore, non-specific SIRS criteria might partly explain the results of present study. Besides, the patients included in the present studies were ASA class I/II. Therefore, although the patients developed SIRS, they were at low risk for developing the clinical consequences such as sepsis or long postoperative hospitalisation stays. The results of the present study were similar to a systematic review that demonstrated that Dex did not affect the ICU length of stay in sepsis patients.[39]

There are some limitations of the present study. First, the study was a single-centre clinical trial. Furthermore, because of the limited medical condition, the overall SIRS incidence rate was very high. The results need to be replicated in different patient populations and be confirmed with large samples as part of a multicentre study. Of note, we only included patients with ASA class I and II. The effect of Dex on SIRS incidences of ASA class III or more severe patients might be explored in the future if necessary. Meanwhile, we did not apply the qSOFA to the present study because the study had started before the qSOFA was introduced. Studies in the future are needed to explore Dex administration on SIRS by using the more specific SIRS criteria, qSOFA. Second, we only explored Dex in PCNL under general anaesthesia. Though the efficacy and safety in PCNL under regional or general anaesthesia are explored in various studies, each anaesthesia technique has its own advantages, with some aspects still being unclear.[40 41] The surgeons in our medical centre are used to performing PCNL under general anaesthesia. The effect of Dex on SIRS in PCNL under regional anaesthesia needs to be explored in the future. Third, the present study only tested the dose recommended by the instructions. Therefore, dose-dependent effects of Dex on SIRS and the underlying mechanisms should be explored in future. Fourth, intraoperative renal pelvic urine and renal stones were not cultured in the present study because all patients received standardised antibiotics perioperatively, which might have affected the clinical outcomes.

In summary, the present study showed that Dex administration during PCNL might be beneficial for decreasing the incidence of SIRS through inhibiting the release of inflammatory mediators, but not clinical consequences such as postoperative hospitalisation duration and costs. Further effects of Dex administration on SIRS in patients who are scheduled for PCNL should be explored in future studies.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval This randomised, double-blinded, prospective parallel study was performed in accordance with the Declaration of Helsinki, approved by the Institutional Review Board of the third affiliated hospital of Sun Yat-sen University (approval number: (2014)2–122).

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Data sharing statement No additional unpublished data are available.

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REFERENCES

1. Pearle MS, Goldfarb DS, Assimos DG, *et al*. Medical management of kidney stones: AUA guideline. *J Urol* 2014;192:316–24.
2. Türk CKT, Petrik A, Sarica K, *et al*. *Guidelines on Urolithiasis 2012*, 2012.
3. Taylor E, Miller J, Chi T, *et al*. Complications associated with percutaneous nephrolithotomy. *Transl Androl Urol* 2012;1:223–8.
4. Labate G, Modi P, Timoney A, *et al*. The percutaneous nephrolithotomy global study: classification of complications. *J Endourol* 2011;25:1275–80.
5. Margel D, Ehrlich Y, Brown N, *et al*. Clinical implication of routine stone culture in percutaneous nephrolithotomy--a prospective study. *Urology* 2006;67:26–9.
6. Korets R, Graversen JA, Kates M, *et al*. Post-percutaneous nephrolithotomy systemic inflammatory response: a prospective analysis of preoperative urine, renal pelvic urine and stone cultures. *J Urol* 2011;186:1899–903.
7. Singh P, Yadav S, Singh A, *et al*. Systemic inflammatory response syndrome following percutaneous nephrolithotomy: assessment of risk factors and their impact on patient outcomes. *Urol Int* 2016;96:207–11.
8. Moses RA, Agarwal D, Raffin EP, *et al*. Postpercutaneous nephrolithotomy systemic inflammatory response syndrome is not associated with unplanned readmission. *Urology* 2017;100:33–7.
9. Gouin JP, Kiecolt-Glaser JK. The impact of psychological stress on wound healing: methods and mechanisms. *Immunol Allergy Clin North Am* 2011;31:81–93.
10. Chen K, Lu Z, Xin YC, *et al*. Alpha-2 agonists for long-term sedation during mechanical ventilation in critically ill patients. *Cochrane Database Syst Rev* 2015;1:CD010269.
11. Schnabel A, Meyer-Frießem CH, Reichl SU, *et al*. Is intraoperative dexmedetomidine a new option for postoperative pain treatment? A meta-analysis of randomized controlled trials. *Pain* 2013;154:1140–9.
12. Ueki M, Kawasaki T, Habe K, *et al*. The effects of dexmedetomidine on inflammatory mediators after cardiopulmonary bypass. *Anaesthesia* 2014;69:693–700.
13. Li B, Li Y, Tian S, *et al*. Anti-inflammatory effects of perioperative dexmedetomidine administered as an adjunct to general anesthesia: a Meta-analysis. *Sci Rep* 2015;5:12342.
14. Sukegawa S, Higuchi H, Inoue M, *et al*. Locally injected dexmedetomidine inhibits carrageenin-induced inflammatory responses in the injected region. *Anesth Analg* 2014;118:473–80.
15. Taniguchi T, Kidani Y, Kanakura H, *et al*. Effects of dexmedetomidine on mortality rate and inflammatory responses to endotoxin-induced shock in rats. *Crit Care Med* 2004;32:1322–6.
16. Yamanaka D, Kawano T, Nishigaki A, *et al*. Preventive effects of dexmedetomidine on the development of cognitive dysfunction following systemic inflammation in aged rats. *J Anesth* 2017;31:25–35.
17. Zhou S, Deng Y, Tan F, *et al*. Retrospective analysis for risk facots of systemic inflammatory response (SIRS) after percutaneous nephrostolithotomy. *Journal of Sun Yat-sen University* 2016;37:295–9.
18. Seyrek M, Binbay M, Yuruk E, *et al*. Perioperative prophylaxis for percutaneous nephrolithotomy: randomized study concerning the drug and dosage. *J Endourol* 2012;26:1431–6.
19. Bag S, Kumar S, Taneja N, *et al*. One week of nitrofurantoin before percutaneous nephrolithotomy significantly reduces upper tract infection and urosepsis: a prospective controlled study. *Urology* 2011;77:45–9.
20. Tan F, Gan X, Deng Y, *et al*. Intraoperative dexmedetomidine attenuates postoperative systemic inflammatory response syndrome in patients who underwent percutaneous nephrolithotomy: a retrospective cohort study. *Ther Clin Risk Manag* 2018;14:287–93.
21. Popat K, Purugganan R, Malik I. Off-label uses of dexmedetomidine. *Adv Anesth* 2006;24:177–92.
22. Brabant SM, Bertrand M, Eyraud D, *et al*. The hemodynamic effects of anesthetic induction in vascular surgical patients chronically treated with angiotensin II receptor antagonists. *Anesth Analg* 1999;89:1388–92.
23. Levy MM, Fink MP, Marshall JC, *et al*. 2001 SCCM/ESICM/ACCP/ATS/SIS International sepsis definitions conference. *Crit Care Med* 2003;31:1250–6.
24. Ganpule AP, Vijayakumar M, Malpani A, *et al*. Percutaneous nephrolithotomy (PCNL) a critical review. *Int J Surg* 2016;36:660–4.
25. Kreydin EI, Eisner BH. Risk factors for sepsis after percutaneous renal stone surgery. *Nat Rev Urol* 2013;10:598–605.
26. Rivera M, Viers B, Cockerill P, *et al*. Pre- and postoperative predictors of infection-related complications in patients undergoing percutaneous nephrolithotomy. *J Endourol* 2016;30:982–6.
27. Aantaa R, Jalonen J. Perioperative use of alpha2-adrenoceptor agonists and the cardiac patient. *Eur J Anaesthesiol* 2006;23:361–72.
28. Ji F, Li Z, Nguyen H, *et al*. Perioperative dexmedetomidine improves outcomes of cardiac surgery. *Circulation* 2013;127:1576–84.
29. Kawasaki T, Kawasaki C, Ueki M, *et al*. Dexmedetomidine suppresses proinflammatory mediator production in human whole blood in vitro. *J Trauma Acute Care Surg* 2013;74:1370–5.
30. Borovikova LV, Ivanova S, Zhang M, *et al*. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature* 2000;405:458–62.
31. Li S, Yang Y, Yu C, *et al*. Dexmedetomidine analgesia effects in patients undergoing dental implant surgery and its impact on postoperative inflammatory and oxidative stress. *Oxid Med Cell Longev* 2015;2015:1–11.
32. Wignall GR, Canales BK, Denstedt JD, *et al*. Minimally invasive approaches to upper urinary tract urolithiasis. *Urol Clin North Am* 2008;35:441–54.
33. Cohen J. The immunopathogenesis of sepsis. *Nature* 2002;420:885–91.
34. Marshall JC. Inflammation, coagulopathy, and the pathogenesis of multiple organ dysfunction syndrome. *Crit Care Med* 2001;29:S99–S106.
35. Churpek MM, Zadravecz FJ, Winslow C, *et al*. Incidence and prognostic value of the systemic inflammatory response syndrome and organ dysfunctions in ward patients. *Am J Respir Crit Care Med* 2015;192:958–64.
36. Finkelsztein EJ, Jones DS, Ma KC, *et al*. Comparison of qSOFA and SIRS for predicting adverse outcomes of patients with suspicion of sepsis outside the intensive care unit. *Crit Care* 2017;21:73.
37. Singer M, Deutschman CS, Seymour CW, *et al*. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;315:801–10.
38. Raith EP, Udy AA, Bailey M, *et al*. Prognostic accuracy of the sofa score, sirs criteria, and qsofa score for in-hospital mortality among adults with suspected infection admitted to the intensive care unit. *JAMA* 2017;317:290–300.
39. Zamani MM, Keshavarz-Fathi M, Fakhri-Bafghi MS, *et al*. Survival benefits of dexmedetomidine used for sedating septic patients in intensive care setting: A systematic review. *J Crit Care* 2016;32:93–100.
40. Hu H, Qin B, He D, *et al*. Regional versus general anesthesia for percutaneous nephrolithotomy: a meta-analysis. *PLoS One* 2015;10:e0126587.
41. Pu C, Wang J, Tang Y, *et al*. The efficacy and safety of percutaneous nephrolithotomy under general versus regional anesthesia: a systematic review and meta-analysis. *Urolithiasis* 2015;43:455–66.