ORIGINAL RESEARCH

Intraoperative dexmedetomidine attenuates postoperative systemic inflammatory response syndrome in patients who underwent percutaneous nephrolithotomy: a retrospective cohort study

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Purpose: Dexmedetomidine (DEX) has been reported to attenuate inflammation in rats. The present retrospective cohort study aimed to investigate whether intraoperative administration with DEX could reduce the incidence of postoperative systemic inflammatory response syndrome (SIRS) in patients following percutaneous nephrolithotomy (PCNL).

Patients and methods: A total of 251 patients were included in the analysis. Among these patients, 175 received intravenous DEX infusion during the intraoperative period and 76 did not. The primary outcome measures were the incidences of postoperative SIRS and fever. Secondary outcomes included patient-controlled analgesia (tramadol) requirements, length of postoperative hospitalization stay, serum creatinine (Scr) and serum blood urea nitrogen (BUN) concentration, and adverse events (bradycardia, hypotension, renal artery thrombosis).

Results: Administration of DEX not only significantly attenuated the incidence of SIRS and fever ($P=0.029$, $P=0.042$, respectively), but also reduced analgesia requirements ($P=0.028$). The length of postoperative hospitalization stay, Scr and BUN concentration, and adverse events did not differ significantly between the two groups. Further univariate and multivariate logistic regression analysis indicated that intraoperative DEX administration was a protective factor against SIRS after PCNL (OR 0.476 [95% CI: 0.257–0.835]; $P=0.019$).

Conclusion: Intraoperative administration of DEX might be associated with reductions in the incidences of SIRS and fever after PCNL.

Keywords: PCNL, SIRS, risk factor, dexmedetomidine

Introduction

Since its initial introduction in 1976,[1] percutaneous nephrolithotomy (PCNL) has become the standard therapy for large renal calculi due to its lower surgical trauma and high stone-free rates. However, postoperative systemic inflammatory response syndrome (SIRS) and sepsis are common complications of the procedure, and can be associated with catastrophic consequences. The incidence of postoperative SIRS of PCNL is reported to range from 9.8 to 43%, which is significantly higher than other endourological surgeries.[2,3] Therefore, investigating strategies to reduce the risk for postoperative SIRS of PCNL is warranted.

Dexmedetomidine (DEX) is a highly selective α_2-adrenergic agonist that has demonstrated sedative, analgesic, and anxiolytic effects.[4,5] Beyond these benefits, emerging

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data show that the medication also exhibits anti-inflammatory properties.[6–9] Treatment with DEX has been shown to attenuate the release of cytokines in cells stimulated by endotoxin in a dose-dependent manner in in vitro studies.[10,11] Specifically, empirical investigations have suggested that DEX has organ-protective effects against ischemia-reperfusion injury in the heart, brain, kidney, and lungs.[9,12–15] In addition, intraoperative infusion of DEX can suppress inflammation and reduce cytokine levels in patients undergoing cardiac surgery.[12] However, the anti-inflammatory effect of DEX has not been studied in patients undergoing PCNL.

To address this knowledge gap, we have retrospectively investigated the association between intraoperative infusion of DEX and the incidence of SIRS and prognosis in patients after PCNL.

Methods
Patients
A total of 415 consecutive adult patients who underwent PCNL at a single center between January 2011 and April 2014 were retrospectively reviewed. Patients who met the following criteria were enrolled in the present analysis: underwent first PCNL surgery; and physical status was evaluated as American Society of Anesthesiologists grade 1 or 2. Exclusion criteria included: age <18 years; combined with tumors, hematopathy, immunosuppressant treatments; diabetes mellitus; preoperative heart rate >90 beats/min; stone diameter <2 cm; heart or kidney disease(s); or preoperative fever. All patient data were extracted from a Hospital Information System database established by the Third Affiliated Hospital. This database is one of the largest all-payer inpatient care databases in the People's Republic of China. In the current study, a total of 251 patients were included in the final analysis.

Ethical standard
This study was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University and was carried out in compliance with the Helsinki Declaration. The requirement for informed consent was waived because of the retrospective nature of the study and using data from which the patients' identification information had been removed.

DEX, anesthesia and analgesia administration
The definition of the DEX administered group was the patient who received a bolus dose 1 µg/kg of DEX after anesthesia induction in no less than 15 min and continuously infused (typically administered it at range from 0.1 to 0.6 µg/kg/h) until 30 min before the end of surgery. The nontreated group (non-DEX) was defined as those who did not receive DEX throughout the perioperative period.

For all PCNL patients, after standard monitoring, induction of general anesthesia consisted of midazolam, fentanyl/sufentanil, propofol and cisatracurium. Maintenance of anesthesia was facilitated with sevoflurane (1%–3%) and oxygen. Ventilation was controlled with 8–10 mL/kg tidal volume with end tidal CO_2 of 35–45 mmHg. Vasoactive drugs including dopamine, dobutamine, nitroglycerine, and phenylephrine were used to maintain blood pressure in normal range according to the hemodynamic responses when necessary, and atropine was used if heart rates were <50 beats/min.

Patients were intravenously infused with flurbiprofen axetil (1 mg/kg) as an analgesic before the end of surgery. Use of flurbiprofen axetil before the end of surgery was routine in our department unless there was a contraindication. If patients had the contraindication of nephrogenic syndrome of inappropriate antidiuresis, 0.05 mg/kg morphine was given alternatively. Tramadol (100 mg) intramuscular injection was administered without pain score assessed when patient complained of a pain after recovery from anesthesia.

Outcome measures
The primary outcome measures included the presence of postoperative SIRS and fever. SIRS definition criteria included a body temperature >38°C or <36°C; a heart rate >90/min; a respiratory rate >20 breaths/min; and a white blood cell count >12,000/mm³ or <4,000 mm³. The presence of ≥2 criteria was accepted as SIRS. Postoperative fever was defined as a body temperature >38.5°C. These primary outcome measures were recorded in the 3-day period after surgery.

In addition, a variety of secondary outcome measures were recorded, including patient-controlled analgesia (tramadol) requirements, postoperative hospital length of stay, serum creatinine (Scr) and serum blood urea nitrogen (BUN) concentration, as well as adverse events including bradycardia, hypotension, and renal artery thrombosis. The postoperative hospital length of stay was defined using the first day after operation and discharge status. Bradycardia was defined as a heart rate <50 beats/min, and hypotension was defined as mean arterial pressure <30% from baseline for 60 s.

Statistical methods
Continuous and categorical variables, respectively, are presented as mean ± standard deviation and percentages.

The Student's *t*-test was used to compare normally distributed variables between the two groups, and the Mann–Whitney U-test was used for non-normally distributed data. Categorical data were compared using the chi-squared or Fisher's exact tests. A multivariable logistic regression (LR) analysis (forward LR method) was used to determine risk factors for SIRS after PCNL; $P < 0.05$ was considered to be statistically significant. All statistical analyses were performed using SPSS version 11.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 251 patients who met the study inclusion criteria were included in the present retrospective analysis. Among these patients, 175 received DEX administration and 76 did not (Figure 1). Demographics and surgical aspects did not differ significantly between groups with and without DEX (Table 1).

Postoperative SIRS was common in this cohort, with an incidence between 0.3% and 21.1% in the first 5 days after PCNL; >90% of these SIRS events occurred in the first 3 days (Figure 2). Similarly, the same trend was observed in postoperative fever events.

Primary and secondary outcomes

In the first 3 days after PCNL, 41 patients in the DEX group developed SIRS, which was a significantly lower proportion than in the non-DEX group (23.4% vs 36.8%, respectively; $P=0.029$) (Table 2). Moreover, the incidence of fever in patients treated with DEX was significantly lower compared with the non-DEX group (16.0% vs 22.4%, respectively; $P=0.042$) (Table 2).

Regarding the analgesic effect of DEX, patient-controlled analgesia (tramadol) requirements in the DEX group were lower than those in the non-DEX group (20% vs 32.9%, respectively; $P=0.028$) (Table 2). The length of postoperative hospitalization stay, and Scr and BUN concentration were not statistically different between the two groups. Similarly, the incidence of adverse events, including bradycardia, hypotension and renal artery thrombosis, did not differ significantly between the two groups (all $P>0.05$) (Table 2).

On univariate and multivariate LR analysis, independent risk factors for the incidence of SIRS were related to operation time and preoperative positive-urine culture (OR 3.011 [95% CI: 1.534–5.911], $P=0.001$; and OR 5.480 [95% CI: 1.666–18.027], $P=0.005$, respectively) (Tables 3 and 4). DEX administration was shown to be a protective factor for SIRS after PCNL (OR 0.476 [95% CI: 0.257–0.835]; $P=0.019$) (Tables 3 and 4).

Discussion

In the present analysis of 251 consecutive patients undergoing PCNL, we found that the intraoperative use of DEX was associated with reduced rates of SIRS after surgery compared with those who did not receive DEX. Moreover, significant reductions in the incidence of postoperative fever and lower requirements for patient-controlled analgesia (tramadol) were observed in patients who received DEX. In addition, multivariable LR analysis further demonstrated that DEX treatment was a protective factor against SIRS. PCNL was identified to be associated with high risk for infection and other complications, with reported rates of up to 83% for total complications.[1] These postoperative complications
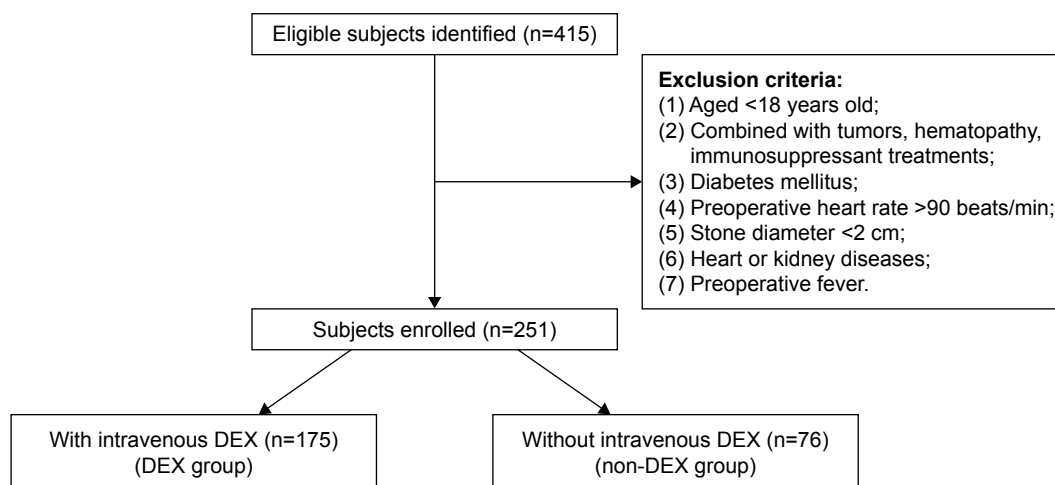
Figure 1 Flow diagram.
Abbreviation: DEX, dexmedetomidine.

Table 1 Demographic and clinical characteristic, stratified by exposure to DEX
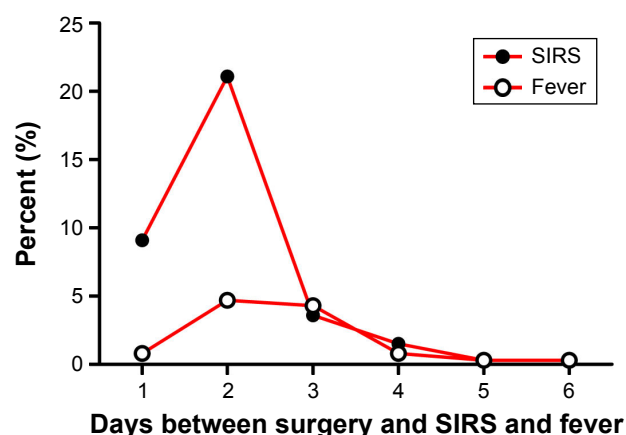
Patient characteristics	DEX (n=175)	Non-DEX (n=76)	P-value
Age (year)	51.87±12.61	48.94±11.67	0.381
Gender (female)	82 (46.9%)	36 (47.4%)	0.941
Weight (kg)	62.28±11.01	59.61±10.19	0.33
ASA grade 2	68 (38.8%)	30 (39.2%)	0.953
Hypertension	27 (15.4%)	16 (21.1%)	0.372
Diabetes	13 (7.5%)	3 (4.0%)	0.231
Surgical history	15 (21.7%)	44 (24.4%)	0.653
Stone diameter (mm)	30.28±10.46	29.75±9.31	0.703
Hydronephrosis	58 (84.1%)	154 (84.6%)	0.913
Staghorn calculus	58 (33.1%)	25 (32.9%)	0.969
Positive-urine culture	8 (4.6%)	6 (7.9%)	0.45
Positive-urine WBC	103 (58.9%)	46 (60.5%)	0.85
Operation time ≥120 min	116 (66.3%)	43 (56.6%)	0.143
Tube size (French)	22.95±5.25	22.66±5.37	0.692
Bloodtransfusion	8 (4.6%)	3 (3.9%)	0.99
Dexamethasone	100 (57.1%)	42 (55.3%)	0.783
Furosemide	72 (41.1%)	26 (34.2%)	0.301

Notes: Data are presented by mean ± standard deviation and n or percentages. Normally distributed variables were compared using Student's t-test, non-normally distributed variables using Mann–Whitney U-test, and categorical data using the chi-squared or Fisher's exact tests; P-value <0.05 was considered significant.
Abbreviations: DEX, dexmedetomidine; ASA, American Society of Anesthesiologists; WBC, white blood cell.

Table 2 Primary and secondary outcome variables

Variables	DEX (n=175)	Non-DEX (n=76)	P-value
SIRS	41 (23.4%)	28 (36.8%)	0.029
Fever (T ≥38.5°C)	28 (16.0%)	17 (22.4%)	0.042
Analgesia tramadol requirements	35 (20.0%)	25 (32.9%)	0.028
Postoperative hospital LOS (d)	9.05±3.86	8.58±2.65	0.502
Scr (μmol/L)	114.04±29.69	121.7±22.48	0.525
BUN (mM/L)	5.93±2.3	5.783±2.0	0.87
Adverse events			
Hypotension	32 (18.3%)	10 (13.2%)	0.317
Bradycardia	10 (5.7%)	7 (9.2%)	0.311
Thrombosis of renal artery	2 (1.1%)	1 (1.3%)	0.38

Notes: Data are presented by mean ± standard deviation and n or percentages. Normally distributed variables were compared using Student's t-test and categorical data using the chi-squared or Fisher's exact tests; P-value <0.05 was considered significant.
Abbreviations: DEX, dexmedetomidine; SIRS, systemic inflammatory response syndrome; LOS, length of stay; Scr, serum creatinine; BUN, serum blood urea nitrogen.

included fever (10.5%–32.1%), SIRS (9.8%–43%), and sepsis (0.3%–4.7%).[1–3,16–18] These events consequently require additional treatment and longer hospital stay; occasionally, severe septic shock leading to death may occur. In the present study, >50% SIRS and fever occurred in the first 3 days after surgery. Consistent with previous studies,[19,20] the overall incidence of SIRS and fever in the first 3 days was 27.5% and 17.9%, respectively.

Previous studies have suggested that several perioperative factors, including positive-urine culture, stone diameter, staghorn calculus, operation time, and blood transfusion, are associated with SIRS after PCNL.[21–24] The present study demonstrated that stone diameter, staghorn calculus, urine culture, operation time, and DEX treatment were factors associated with SIRS after PCNL. Preoperative positive-urine culture and operative time were identified as independent risk factors for SIRS. We have speculated that increased fluid and toxins translocated into the systemic circulation with

Figure 2 Days between surgery and SIRS and fever.
Abbreviation: SIRS, systemic inflammatory response syndrome.

Table 3 Univariate logistic regression results for post-PCNL SIRS

Patient characteristics	OR	95% CI	P-value
Age	1.774	0.946–3.329	0.074
Gender (female)	1.330	0.763–2.318	0.314
ASA	0.795	0.466–1.355	0.399
Hypertension	1.013	0.488–2.103	0.972
Diabetes	0.856	0.267–2.752	0.795
Surgical history	0.871	0.448–1.694	0.685
Stone diameter	3.997	1.224–13.053	0.022
Hydronephrosis	0.959	0.448–2.050	0.913
Staghorn calculus	1.872	1.055–3.322	0.032
Urine culture	5.310	1.712–16.467	0.004
Urinary infection	1.444	0.559–3.728	0.448
Operation time	2.640	1.388–5.023	0.003
Tube size (French)	1.017	0.965–1.071	0.527
Blood transfusion	0.989	0.255–3.840	0.987
Dexamethasone	1.082	0.618–1.895	0.783
Furosemide	1.290	0.735–2.264	0.376
Vasoactive agent	0.794	0.367–1.718	0.559
DEX administration	0.525	0.293–0.939	0.03

Notes: Univariate logistic regression analysis (forward LR method) was used to determine risk factors for SIRS after PCNL; P<0.05 was considered to be statistically significant.
Abbreviations: PCNL, percutaneous nephrolithotomy; SIRS, systemic inflammatory response syndrome; ASA, American Society of Anesthesiologists; DEX, dexmedetomidine; LR, logistic regression.

Table 4 Multivariate logistic regression results for post-PCNL SIRS

Patient characteristic	OR	95% CI	*P*-value
Operation time	3.011	1.534–5.911	0.001
Urine culture	5.480	1.666–18.027	0.005
DEX administration	0.476	0.257–0.835	0.019

Notes: Multivariable logistic regression analysis (forward LR method) was used to determine risk factors for SIRS after PCNL; *P*<0.05 was considered to be statistically significant.
Abbreviations: PCNL, percutaneous nephrolithotomy; SIRS, systemic inflammatory response syndrome; DEX, dexmedetomidine; LR, logistic regression.

prolonged durations of surgery could subsequently result in high incidences of postoperative SIRS. However, Caddedu et al reported that there were no clear correlations between duration of surgery and the incidence of postoperative fever.[25] Different criteria may contribute to these differences. Studies have identified the significance of perioperative urine culture for infection after PCNL.[26,27] Results of present study suggest that perioperative urine culture is an independent risk factor for postoperative SIRS. Consequently, clinicians should consider the use of preoperative antibiotics for patients who present with positive-urine culture(s). Interestingly, results of the current study also suggest that DEX administration is a protective factor against the development of SIRS after PCNL. It would be reasonable to speculate that intraoperative DEX treatment may be an effective strategy for reducing the risk for postoperative SIRS after PCNL.

DEX is highly selective α_2-adrenergic agonist, and is widely used for anxiolysis, sedation, and analgesia.[4,5] Recently, studies have demonstrated the protective benefits of DEX, which are exerted through its anti-inflammatory properties.[6–9] Administration of DEX could alleviate systemic inflammation in animals through stabilization of the sympathetic nervous system.[28,29] DEX significantly reduced ischemia/reperfusion damage in diabetic rats, and the mechanism may be related to down-regulated expression of pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin-6.[30] Our previous study has demonstrated that DEX had protected against acute kidney injury by down-regulating inflammatory reactions in endotoxemia.[31] In clinical practice, DEX has demonstrated its anti-inflammatory effects in cardiac surgery, where it has significantly reduced sepsis in patients with cardiac disease by suppressing the production of pro-inflammatory cytokines.[12,13] Moreover, it has also produced neuroprotective effects by attenuating inflammation and oxidative stress.[32] In the present retrospective analysis, >50% of the patients who underwent PCNL received intraoperative administration of DEX, which was associated with a lower incidence

of postoperative SIRS and fever after PCNL compared with those who did not receive DEX. Furthermore, as commonly reported about the inflammation and neuropathic pain after PCNL, the results of our study supported the analgesic benefit of DEX. Patient-controlled analgesia (tramadol) requirements were significantly lower in the DEX group than in the non-DEX group. Beyond its anti-inflammatory properties, DEX also produces its analgesic effect by central and spinal cord α_2 receptor modulation.[33] Of note, these benefits did not result in a better prognosis because the length of postoperative hospital stay was similar regardless of whether patients received DEX. Consistent with our results, a previous study also suggested that DEX could decrease the incidence of sepsis, but could not reduce the length of hospital stay.[13] This would be reasonable because many patient-specific factors are associated with postoperative hospital length of stay.

Beyond its reported protective effects, attention should be devoted to the fact that DEX infusion may result in bradycardia and hypotension due to decreased sympathetic tone and increased vagal activity. Furthermore, Scheinin et al reported that young volunteers exhibited bradycardia and sinus arrest with infusion of DEX.[34] However, in the present study, we found that the incidence of hypotension and bradycardia were similar in our patients, regardless of whether they received DEX. Intraoperative stress may compensate for this discrepancy. It has been reported that unaltered hemodynamics has been recorded in patients even with high doses of DEX.[35,36]

There were several limitations to the current study, the first of which was its retrospective cohort design. Although multivariate regression analysis was used without any apparent adjustment to reduce evident biases, potential confounding biases are inherent because this was a nonrandomized study. Second, the number of patients treated with DEX is more than twice those untreated. The total number of participants was small. Thus, study with large number is needed in future. Thirdly, many perioperative factors were associated with SIRS after PCNL; therefore, the exact role of DEX in postoperative SIRS and fever remains to be determined, preferably in further prospective studies. Finally, this was a single-institution study and, as such, was limited by the involvement of different surgeons, surgical techniques, and treatment protocols, which may have impacted the results.

Conclusion

Collectively, findings from the current study suggest that intraoperative administration of DEX might be associated with reductions in the incidence of SIRS and fever after

PCNL, as well as lower requirements for patient-controlled analgesia (tramadol). However, these results are only hypothesis-generating, and a large, well-conducted randomized controlled trial is required to confirm the exact role DEX plays in postoperative SIRS and fever.

Acknowledgments

Author contributions

Shaoli Zhou, Zhuang-Gui Chen, and Qianqian Zhu, helped design the study, conduct of the study and prepared the manuscript. Fang Tan helped data collection, data analysis, and manuscript preparation. Xiaoliang Gan helped manuscript preparation. Xiaoyun Li, Yingqing Deng, Na Guo, and Ziqing Hei helped data collection and data analysis. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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