ORIGINAL ARTICLES

UDC: 616.61-089.843-089.168::616.8-009.7-085
DOI: https://doi.org/10.2298/VSP231103057M

Effects of sufentanil in combination with dexmedetomidine for patient-controlled intravenous analgesia after renal transplantation

Efekti sufentanila u kombinaciji sa deksmedetomidinom za intravensku analgeziju koju kontroliše bolesnik posle transplantacije bubrega

Jun Ma*, Yawen Yang†, Linhao Sun†, Tingting Wu†

***Wuhan Wuchang Hospital, Department of Anesthesiology, Wuhan, China; †Soochow University, First Affiliated Hospital, Department of Anesthesiology, Suzhou, China**

Abstract

Background/Aim. Nowadays, the most convenient analgesic method is patient-controlled intravenous injection of one or more adjuvant drugs. The aim of our study was to evaluate the effects of sufentanil plus dexmedetomidine for patient-controlled intravenous analgesia (PCIA) after renal transplantation. **Methods**. Seventy-eight patients receiving living-related renal transplantation under general anesthesia were selected. Radioisotope scanning was performed, and the single glomerular filtration rate of the unilateral kidney was ≥ 40 mL/min/1.73 m². The control group (CG) and observation group (OG) (39 patients in each group) were analgesic with sufentanil and sufentanil plus dexmedetomidine, respectively. When the Visual Analogue Scale (VAS) score exceeded 4 points, 0.05 mg/kg oxycodone was intravenously injected for remedial analgesia. Plasma levels of endothelin, urea nitrogen, and creatinine were measured by radioimmunoassay. Heart rate (HR), mean arterial pressure, oxygen saturation, VAS score, and sedation score were recorded before anesthesia and after surgery. Analgesic remediation rate, number of effectively pressing the PCIA pump, and incidence rate of adverse reactions within 48 hrs after surgery were recorded. **Results**. HR of OG was significantly lower than that of CG 6 and 12 hrs after surgery ($p < 0.05$). VAS score of OG was lower than that of CG 6, 12, and 24 hrs after surgery ($p < 0.05$). OG had a lower postoperative remedial rate, number of effectively pressing the PCIA pump, and incidence rates of nausea and vomiting ($p < 0.05$) compared to CG. Endothelin, urea nitrogen, and creatinine levels significantly decreased after surgery compared with those before anesthesia ($p < 0.05$). The levels of OG were lower than those of CG at each time point after surgery ($p < 0.05$). **Conclusion**. Sufentanil plus dexmedetomidine can be safely and effectively used for PCIA after renal transplantation, with superior outcomes to those of sufentanil alone.

Key words:
analgesia; analgesia, patient-controlled; anesthesia, intravenous; kidney transplantation; postoperative period.

Apstrakt

Uvod/Cilj. Intravenska injekcija jednog ili više pomoćnih lekova, koju kontroliše bolesnik, najpouzdanija je analgetska metoda u današnje vreme. Cilj rada bio je da se proceni efekat sufentanila u kombinaciji sa deksmedetomidinom za intravensku analgeziju koju kontroliše bolesnik (*patient-controlled intravenous analgesia* – PCIA), nakon transplantacije bubrega. **Metode.** Izvršena je selekcija 78 bolesnika kojima je u opštoj anesteziji izvršena transplantacija bubrega živog davaoca. Urađeno je skeniranje radioizotopima, a pojedinačna stopa glomerulske filtracije jednog bubrega bila je ≥ 40 mL/min/1.73 m². Ispitanici iz kontrolne grupe (KG) i posmatrane grupe (PG) (po 39 bolesnika u obe grupe) primili su u cilju analgezije sufentanil i sufentanil sa deksemedetomidinom, redom. Kada je skor Vizuelne analogne skale (VAS) bio iznad 4 poena, intravenski je injektirano 0,05 mg/kg oksikodona za dodatnu analgeziju. Nivoi endotelina, uree i kreatinina u plazmi mereni su radioimunoesejem. Frekvencija srčanog rada (*heart rate* – HR), srednji arterijski pritisak, saturacija kiseonikom, skor VAS i skor sedacije beleženi su pre anestezije i posle operacije. Zabeleženi su stopa dodavanja analgetika, broj efektivnog pritiska PCIA pumpe i stopa incidencije neželjenih reakcija tokom 48 sati posle operacije. **Rezultati.** Nađena je značajno niža HR kod PG u odnosu na KG 6 i 12 sati posle operacije ($p < 0,05$). Skor VAS u PG bio je niži nego u KG 6, 12 i 24 sata posle operacije ($p < 0,05$). Kod PG utvrđena je niža stopa postoperativnog dodavanja leka, broja efektivnih pritisaka na PCIA pumpu i stope incidencije mučnine i povraćanja, u odnosu na KG ($p < 0,05$). Nivoi endotelina, uree i kreatinina su se značajno snizili posle operacije, u poređenju sa nivoima pre anestezije ($p < 0,05$). Nivoi u PG bili su niži od nivoa u KG na svakoj posmatranoj tački posle operacije ($p < 0,05$).

Correspondence to: Yawen Yang, First Affiliated Hospital of Soochow University, Department of Anesthesiology, No. 188 Shizi Road, Suzhou 215000, Jiangsu Province, China. Email: wrrdr5725zlxa@163.com

Zaključak. Sufentanil u kombinaciji sa deksmedetomidinom se može bezbedno i efikasno koristiti za PCIA posle transplantacije bubrega, sa uspešnijim ishodom u odnosu na primenu samog sufentanila.

Ključne reči:
analgezija; analgezija, kontrolisana od strane bolesnika; anestezija, intravenska; transplantacija bubrega; postoperativni period.

Introduction

Chronic renal failure is an irreversible disease that develops over a long period of time. With the prolongation of life expectancy and the increasing incidence of chronic diseases, such as hypertension and diabetes mellitus, the incidence rate of chronic renal failure is on the rise [1]. Kidney transplantation is the best therapy for patients with end-stage renal disease. This method has lower costs and fewer complications than long-term hemodialysis, and it can also improve patients' survival and quality of life [2]. Most patients suffer from end-stage renal disease, i.e., uremia. In addition to renal failure, the patients also suffer from other complications concerning other organ dysfunction and serious complica-tions, such as hypertension, water retention, electrolyte imbalance, acid-base imbalance, cardiac insufficiency, blood coagulation abnormality, metabolic and endocrine disorders, and nervous system diseases. Given the pathological, physiological, pharmacokinetics, and pharmacodynamics characteristics of end-stage renal failure, patients are less tolerant to anesthesia and analgesia in surgery [3, 4]. Therefore, it is of great significance to select appropriate anesthetic methods and drugs for patients receiving renal transplantation.

Sufentanil exerts a central analgesic effect by acting on μ and K receptors [5]. Nie et al. [6] used postoperative patient-controlled intravenous analgesia (PCIA) with sufentanil for women undergoing cesarean section. Although the analgesic effects were satisfactory, patients had adverse reactions (AR) such as nausea, vomiting, lethargy, and respiratory depression during follow-up because the dose of sufentanil was too high, but a lower dose led to insufficient analgesia. Currently, the most convenient and reasonable analgesic method is patient-controlled intravenous injection of one or more adjuvant drugs [7]. Dexmedetomidine (DEX) binds α-2 adrenergic receptors in the brainstem *nucleus coeruleus* to inhibit the transmission of pain signals to the brain and produce analgesic effects at the central level [8, 9]. It is now an adjuvant drug for anesthesia and pain management [10, 11]. The combination of sufentanil and DEX (SDEX), although the dose of each drug is lower than that of the single-use, takes a synergistic effect [12]. Meanwhile, sufentanil can enter the central nervous system through active transport. The concentration of unbound sufentanil in brain tissue is higher, and the pharmacodynamic effect is stronger, which makes up for the defect of low affinity for μ opioid receptor [13].

This study was designed to evaluate the efficacy of SDEX for PCIA after renal transplantation.

Methods

Baseline clinical data

Seventy-eight patients receiving living-related renal transplantation under general anesthesia from December 2020 to December 2022 were selected. This study has been approved by the Ethics Committee of the First Affiliated Hospital of Soochow University (from December 5, 2020), and written informed consent has been obtained from all donors and recipients. Kidney donors were determined eligible based on the Consensus Statement of the Amsterdam Forum on the Care of the Live Kidney Donor (2004). Absolute and relative contraindications of living donors were excluded. Radioisotope scanning was performed, and the single glomerular filtration rate of the unilateral kidney was ≥ 40 mL/min/1.73 m^2.

Inclusion criteria were as follows: 1) patients aged 20–50 years, the American Society of Anesthesiologists class II–III, and body weight not exceeding or lower than 20% of the standard one; 2) patients receiving regular preoperative hemodialysis, with the time from last dialysis to surgery of 12–36 hrs; 3) patients receiving preoperative treatment with diabetic agents, and preoperative fasting blood glucose level of < 10 mmol/L; 4) patients without abnormalities of other routine examinations or heart and lung functions before surgery.

Exclusion criteria were: 1) patients with severe cardiac and pulmonary dysfunction, vital organ insufficiency, difficulty in tolerating surgery, severe anemia (hemoglobin < 7 g/dL), or diseases related to nerve or neuromuscular transmission function; 2) patients with blood coagulation abnormality, respiratory failure and history of renal transplantation; 3) patients with communication difficulties (language/physical defects/culture) affecting information collection.

The patients were divided into two groups (39 patients each) using the random number table method. The control group (CG) was analgesic with sufentanil, and the observation group (OG) was given SDEX. Medical staff who did not participate in this study connected and set the PCIA pump and observed related postoperative indicators. PCIA was performed by the researchers of this study immediately after surgery.

Anesthesia methods

Penehyclidine hydrochloride (0.5 mg) was intramuscularly injected 30 min before anesthesia. The venous access of the upper extremity was opened, and sodium acetate – Ringer's solution was infused at 5 mL/min. The opposite iliac artery was catheterized under local anesthesia. Blood pressure, heart rate (HR), central venous pressure, electrocardiogram,

and oxygen saturation (SpO_2) were routinely monitored. The bispectral index (BIS) was continuously monitored using the Aspect A-1000 BIS monitor.

Anesthesia induction: each patient was sequentially intravenously (i.v.) injected with 0.05 mg/kg midazolam, 1.5–2.0 mg/kg propofol, 0.3 μg/kg sufentanil, and 0.2 mg/kg cisatracurium besylate. After tracheal intubation, mechanical ventilation was performed to maintain partial pressure of end-tidal (P_{ET}) CO_2 of 35~40 mmHg (1 mmHg = 0.133 kPa) and SpO_2 of 95%~98%

Anesthesia maintenance: each patient was subjected to inhalation of 1–2% sevoflurane as well as i.v. infusion of 4–6 mg/kg/h propofol, 5–10 μg/kg/h remifentanil, and 0.1 mg/kg/h cisatracurium besylate to maintain the fluctuations of HR and mean arterial pressure (MAP) within 20% of the baseline values. BIS was maintained at 40–60. Sevoflurane, remifentanil, and cisatracurium besylate were discontinued 30 min before surgery, and propofol was stopped at the end of surgery. After surgery, 5 mg tropisetron and 0.1 mg/kg oxycodone were i.v. administered for both groups. A PCIA pump was connected immediately after surgery. The endotracheal tube was removed after the patients woke up naturally and had indications for extubation. CG was given 1.5 μg/kg sufentanil and 5 mg tropisetron dissolved in 100 mL of normal saline, and OG was given 1.5 μg/kg sufentanil, 2 μg/kg DEX hydrochloride, and 5 mg tropisetron dissolved in 100 mL of normal saline. The background infusion rate was 2 mL/h, the PCIA dose was 0.5 mL/time, and the lockout time was 15 min. The PCIA pump was used continuously for 48 hrs to maintain a VAS score of ≥ 4 points. When the VAS score exceeded > 4 points, 0.05 mg/kg oxycodone was i.v. injected for remedial analgesia.

Observation indices

Venous blood was collected before anesthesia and 24, 48, and 72 hrs after surgery. The levels of plasma endothelin, urea nitrogen, and creatinine were measured by radioimmunoassay. HR, MAP, SPO_2, VAS score, and sedation score were recorded before anesthesia and 2, 6, 12, 24, and 48 hrs after surgery.

The analgesic remediation and number of effectively pressing the PCIA pump within 48 hrs after surgery were recorded. AR within 48 hrs after surgery, such as oversedation (Ramsay score: ≤ 4 points), nausea, vomiting, dizziness, respiratory depression, and catheterization-induced bladder irritation, were recorded.

Statistical analysis

All data were analyzed by SPSS 16.0 software. The normally distributed measurement data were represented as mean ± standard deviation. Intergroup comparisons at various time points were performed by the repeated measures analysis of variance data. In case of significant intergroup differences, intergroup comparisons at each time point were conducted with the Independent Samples *t*-test. The time differences between groups were compared using the Student-Newman-Keuls q (SNK-q) test. The numerical data were subjected to the Chi-square (χ^2) test. The ranked data were compared with the rank sum test; $p < 0.05$ was considered statistically significant.

Results

Baseline clinical data and surgical outcomes

The two groups had similar baseline clinical data and surgical outcomes, including surgical time, anesthesia time, intraoperative blood loss, and intraoperative fluid transfusion volume ($p > 0.05$) (Table 1).

MAP, HR, and SpO_2 at different time points

The MAP values of the two groups decreased after surgery compared with those before anesthesia ($p > 0.05$). HR of OG was significantly lower than that of CG 6 and 12 hrs after surgery ($p < 0.05$). At each time point after surgery, the SpO_2 values of the two groups were maintained at above 95%, without significant intergroup differences ($p > 0.05$) (Table 2).

VAS and Ramsay scores at different time points

The VAS score of OG was significantly lower than that of CG 6, 12, and 24 hrs after surgery ($p < 0.05$). There was no statistically significant difference in Ramsay's score between the two groups ($p > 0.05$) (Table 3).

Table 1

Baseline clinical data and surgical outcomes in patients who underwent renal transplantation

Parameter	Control group	Observation group	*t* or χ^2 value	*p*-value
Age, year	45.67 ± 5.67	45.78 ± 5.98	$t = 0.431$	0.667
Body weight, kg	58.35 ± 4.38	58.29 ± 4.41	$t = 0.512$	0.613
BMI, kg/m^2	22.88 ± 2.48	23.02 ± 2.51	$t = 0.601$	0.549
Gender ratio (male/female)	26/13	25/14	$\chi^2 = 0.325$	0.567
ASA class II/III	33/6	32/7	$\chi^2 = 0.247$	0.618
Surgical time, min	153.78 ± 19.87	154.37 ± 20.22	$t = 1.379$	0.170
Anesthesia time, min	157.13 ± 24.38	156.96 ± 23.28	$t = 1.245$	0.216
Intraoperative blood loss, mL	189.23 ± 19.29	192.35 ± 21.29	$t = 1.315$	0.191
Intraoperative fluid transfusion volume, mL	1568.97 ± 109.97	1571.78 ± 112.45	$t = 1.110$	0.269

ASA – American Society of Anesthesiologists. n = 39 patients in each group.
All values are given as mean ± standard deviation or numbers.

Analgesic remediation, number of effectively pressing the PCIA pump, and incidence rate of adverse reactions within 48 hrs after surgery

Compared with the CG, the postoperative remedial rate, number of effectively pressing the PCIA pump, and incidence rates of nausea and vomiting were significantly lower in OG than in CG within 48 hrs after surgery ($p < 0.05$). However, they had similar incidence rates of catheter-related bladder irritation and dizziness ($p > 0.05$) (Table 4).

Levels of plasma endothelin, urea nitrogen, and creatinine

The levels of endothelin, urea nitrogen, and creatinine significantly decreased at all-time points after surgery

Table 2

MAP, HR, and SpO_2 at different time points

Parameter	Before	Postoperative				
		2 hrs	6 hrs	12 hrs	24 hrs	48 hrs
MAP, mmHg						
CG	117.94 ± 18.35	108.79 ± 17.37	104.78 ± 16.01	99.23 ± 15.89	98.64 ± 16.78	98.79 ± 16.93
OG	117.61 ± 18.29	110.68 ± 17.24	102.78 ± 15.79	98.25 ± 16.94	98.57 ± 17.01	97.16 ± 17.02
t-value	0.503	0.773	0.204	0.088	0.201	0.006
p-value	0.614	0.443	0.837	0.769	0.652	0.947
HR, bpm						
CG	79.46 ± 12.04	78.82 ± 12.43	98.45 ± 13.24	99.35 ± 13.12	79.45 ± 11.28	78.23 ± 12.34
OG	78.79 ± 11.89	77.81 ± 11.78	75.48 ± 12.23*	76.27 ± 12.47*	78.29 ± 11.76	77.69 ± 12.04
t-value	0.452	0.172	3.445	3.246	0.228	0.017
p-value	0.651	0.865	0.001	0.003	0.643	0.896
SpO_2, %						
CG	96.82 ± 1.17	96.76 ± 1.39	96.24 ± 1.25	96.52 ± 1.31	96.42 ± 1.54	96.56 ± 1.43
OG	96.78 ± 1.23	96.85 ± 1.25	97.48 ± 1.23	96.29 ± 1.19	96.54 ± 1.29	96.82 ± 1.34
t-value	0.474	0.197	0.351	0.242	0.373	0.021
p-value	0.635	0.842	0.724	0.811	0.708	0.793

MAP – mean arterial pressure; HR – heart rate; SpO_2 – oxygen saturation; CG – control group; OG – observation group. n = 39 patients in each group. All values are given as mean ± standard deviation.
***Intergroup comparison at the same time point, $p < 0.05$.**

Table 3

VAS and Ramsay scores at different time points

Parameter	Postoperative				
	2 hrs	6 hrs	12 hrs	24 hrs	48 hrs
VAS score					
CG	1.25 ± 0.23	2.97 ± 0.38	2.71 ± 0.36	2.53 ± 0.38	1.71 ± 0.41
OG	1.14 ± 0.18	1.26 ± 0.35*	1.09 ± 0.32*	1.34 ± 0.31*	1.48 ± 0.39
t-value	0.351	4.341	4.769	4.947	0.375
p-value	0.724	0.001	0.001	0.001	0.710
Ramsay score					
CG	2.18 ± 0.43	2.11 ± 0.39	2.36 ± 0.34	2.27 ± 0.32	2.21 ± 0.29
OG	2.17 ± 0.42	2.24 ± 0.41	2.29 ± 0.41	2.22 ± 0.33	2.19 ± 0.31
t-value	0.240	0.476	0.197	0.454	0.170
p-value	0.809	0.637	0.842	0.653	0.863

VAS – Visual Analog Scale; For other abbreviations, see Table 2. n = 39 patients in each group.
All values are given as mean ± standard deviation. *Intergroup comparison at the same time point, $p < 0.05$.

Table 4

Analgesic remediation, number of effectively pressing the PCIA pump, and incidence rate of adverse reactions within 48 hrs after surgery

Parameter	Control group	Observation group	*t* or χ^2 value	*p*-value
Analgesic remediation rate, %	20.51	2.56*	$\chi^2 = 4.805$	0.001
Number of effectively pressing the PCIA pump	7.82 ± 1.19	1.84 ± 0.43*	$t = 3.971$	0.008
Incidence rate, n				
of nausea	20.51	7.69*	$\chi^2 = 0.851$	0.048
of vomiting	12.82	2.56*	$\chi^2 = 5.651$	0.001
of catheter-related bladder irritation	2.56	0	–	–
of dizziness	12.82	10.26	$\chi^2 = 0.211$	0.644

PCIA – patient-controlled intravenous analgesia. n = 39 patients in each group.
Values for the number of effectively pressing the PCIA pump are given as mean ± standard deviation.
***Intergroup comparison at the same time point, $p < 0.05$.**
Note: *t* or χ^2 and *p*-value for incidence rate of catheter-related bladder irritation cannot be calculated due to zero value.

Table 5

Levels of plasma endothelin, urea nitrogen, and creatinine

Parameter	Before	Postoperative		
		24 hrs	48 hrs	72 hrs
Endothelin, ng/L				
CG	129.76 ± 18.57	98.71 ± 13.39#	91.71 ± 11.23#	87.56 ± 11.85#
OG	128.74 ± 18.47	86.45 ± 13.45*#	79.65 ± 11.54*#	72.29 ± 12.76*#
Urea nitrogen, mmol/L				
CG	17.41 ± 1.74	10.45 ± 1.92#	9.49 ± 1.75#	6.98 ± 1.48#
OG	17.31 ± 1.84	7.74 ± 1.86*#	6.89 ± 1.22*#	4.67 ± 0.37*#
Creatinine, mmol/L				
CG	977.12 ± 81.43	467.72 ± 81.45#	376.21 ± 61.21#	196.89 ± 51.31#
OG	976.14 ± 81.25	334.81 ± 82.23*#	219.41 ± 54.17*#	104.33 ± 49.13*#

CG – control group; OG – observation group. n = 39 patients in each group.
All values are given as mean ± standard deviation. *Intergroup comparison at the same time point after surgery, $p < 0.05$; #compared with the same group before surgery, $p < 0.05$.

compared with those before surgery ($p < 0.05$). The levels of OG were significantly lower than those of CG at each time point after surgery ($p < 0.05$) (Table 5).

Discussion

Postoperative pain (PP) is a complex physiological and psychological reaction caused by noxious stimulation [14, 15]. Multimodal analgesia is a combined use of analgesic drugs with different mechanisms of action or different analgesic measures to produce analgesic effects through multiple routes to obtain better effects and reduce AR [16]. Notably, PCIA can better alleviate PP using combined analgesic drugs [17]. In this study, SDEX was used for PCIA, and the results showed that the VAS scores at 6, 12, and 24 hrs after combined use were significantly lower than those of sufentanil alone, which is consistent with previous literature [18].

When used for postoperative analgesia, opioids, such as sufentanil, may often cause AR-like respiratory depression, nausea and vomiting, and excessive sedation despite good analgesic effects [19]. If the dosage of the drugs is not controlled well, it may further increase postoperative risk. Unlike opioids, DEX can work effectively without inducing respiratory depression [20]. In this study, the postoperative remediation rate and PCIA effective compression times also decreased. In addition, the incidence rate of nausea and vomiting was also significantly lower, and the HR values at 6 and 12 hrs after surgery of the SDEX were significantly lower than those of the sufentanil group. Likewise, Tang et al. [21] reported that SDEX worked better than sufentanil alone in alleviating PP, inflammation, and delirium after esophageal cancer surgery. Plasma endothelin is synthesized by endothelial cells and is significantly elevated under stress conditions such as pain and anxiety, which, therefore, is considered to be a sensitive index of stress response [22]. When renal function is severely impaired, plasma endothelin increases, further causing contraction of renal blood vessels, reduced renal blood flow, and glomerular filtration rate, thereby reducing urine output [23]. Besides, the abundance of urea nitrogen is a well-established substitute marker for renal function. During a stress response, the production of urea nitrogen is promoted, finally leading to the increase in blood level [24]. Moreover, creatinine is excreted by renal metabolism, so its level in plasma is elevated when the renal function is damaged, especially in the case of stress response [25]. PCIA can effectively alleviate pain and reduce stress response in renal transplant patients [26]. Herein, plasma endothelin, urea nitrogen, and creatinine levels in OG were significantly lower than those in CG 24 hrs after surgery. The findings are in agreement with those of a previous study [27].

Conclusion

In conclusion, sufentanil combined with dexmedetomidine can be safely and effectively used for PCIA after renal transplantation, with an effect better than that of sufentanil alone.

Conflict of interests

The authors declare no conflict of interest.

R E F E R E N C E S

1. *Kotsis F, Bächle H, Altenbuchinger M, Dönitz J, Njipouombe Nsangou YA, Meiselbach H,* et al. Expectation of clinical decision support systems: a survey study among nephrologist end-users. BMC Med Inform Decis Mak 2023; 23(1): 239.
2. *Shaheen FAM, Al-Attar B, Ahmad MK, Follero PM.* Burden of disease: Prevalence and incidence of endstage renal disease in Middle Eastern countries. Clin Nephrol 2020; 93(1): 120–3.
3. *Saumoy M, Jesudian AB, Aden B, Serur D, Sundararajan S, Sivananthan G,* et al. High prevalence of colon adenomas in end-stage kidney disease patients on hemodialysis undergoing renal transplant evaluation. Clin Transplant 2016; 30(3): 256–62.
4. *Al-Rashid F, Bienholz A, Hildebrandt HA, Patsalis PC, Totzeck M, Kribben A,* et al. Transfemoral transcatheter aortic valve implantation in patients with end-stage renal disease and kidney transplant recipients. Sci Rep 2017; 7(1): 14397.
5. *Wei S, Qiu CY, Jin Y, Liu TT, Hu WP.* Dexmedetomidine Inhibits ASIC Activity via Activation of α_{2A} Adrenergic Receptors in Rat Dorsal Root Ganglion Neurons. Front Pharmacol 2021; 12: 685460.

6. *Nie Z, Cui X, Zhang R, Li Z, Lu B, Li S,* et al. Effectiveness of Patient-Controlled Intravenous Analgesia (PCIA) with sufentanil background infusion for post-cesarean analgesia: a randomized controlled trial. J Pain Res 2022; 15: 1355–64.
7. *Emons MI, Maring M, Stamer UM, Pogatzki-Zahn E, Petzke F, Erlenwein J.* Safety and monitoring of patient-controlled intravenous analgesia: Clinical practice in German hospitals. Anaesthesist 2021; 70(6): 476–85. (German)
8. *Nie Y, Tu W, Shen X, Yu W, Yu Y, Song X,* et al. Dexmedetomidine added to sufentanil patient-controlled intravenous analgesia relieves the postoperative pain after cesarean delivery: a prospective randomized controlled multicenter study. Sci Rep 2018; 8: 9952.
9. *Kim J, Choi SM, Park YS, Lee CH, Lee SM, Yoo CG,* et al. Dexmedetomidine versus midazolam for sedation during endobronchial ultrasound-guided transbronchial needle aspiration: A randomised controlled trial. Eur J Anaesthesiol 2021; 38(5): 534–40.
10. *Karthik NM, Das SG, Johney J, George M, Issac E, Vasudevan A.* Comparison of postoperative analgesia with two different doses of dexmedetomidine as an adjuvant to ropivacaine in adductor canal block for unilateral total knee replacement surgery: A randomized double-blinded study. J Anaesthesiol Clin Pharmacol 2022; 38(3): 428–33.
11. *Bielka K, Kuchyn I, Babych V, Martycshenko K, Inozemtsev O.* Dexmedetomidine infusion as an analgesic adjuvant during laparoscopic cholecystectomy: a randomized controlled study. BMC Anesthesiol 2018; 18(1): 44.
12. *Feng M, Chen X, Liu T, Zhang C, Wan L, Yao W.* Dexmedetomidine and sufentanil combination versus sufentanil alone for postoperative intravenous patient-controlled analgesia: a systematic review and meta-analysis of randomized controlled trials. BMC Anesthesiol 2019; 19(1): 81.
13. *Han C, Lei D, Jiang W, Ren H, Su G, Feng S,* et al. Pre-emptive dexmedetomidine decreases the incidence of chronic post hysterectomy pain. Int J Clin Exp Med 2019; 12(1): 967–71.
14. *Fernandez Rojas R, Brown N, Waddington G, Goecke R.* A systematic review of neurophysiological sensing for the assessment of acute pain. NPJ Digit Med 2023; 6(1): 76.
15. *May ES, Tiemann L, Schmidt P, Nickel MM, Wiedemann N, Dresel C,* et al. Behavioral responses to noxious stimuli shape the perception of pain. Sci Rep 2017; 7: 44083.
16. *Wick EC, Grant MC, Wu CL.* Postoperative Multimodal Analgesia Pain Management with Nonopioid Analgesics and Techniques. JAMA Surg 2017; 152(7): 691–7.
17. *Deshler BJ, Rockenbach E, Patel T, Monahan BV, Poggio JL.* Current update on multimodal analgesia and nonopiate surgical pain management. Curr Prob Surg 2023; 60(6): 101332.
18. *Jiang H, Zheng Y, Liu C, Bao Y.* Postoperative analgesia effects of sulfentanyl plus dexmedetomidine in patients received VATS. Pteridines 2020; 31(1): 55–60.
19. *García-López C, Gómez-Huertas C, Sánchez-González JM, Borroni D, Rodríguez-Calvo-de-Mora M, Romano V,* et al. Opioids and Ocular Surface Pathology: A Literature Review of New Treatments Horizons. J Clin Med 2022; 11(5): 1424.
20. *Oshima H, Nakamura M, Watanabe O, Yamamura T, Funasaka K, Ohno E,* et al. Dexmedetomidine provides less body motion and respiratory depression during sedation in double-balloon enteroscopy than midazolam. SAGE Open Med 2017; 5: 2050312117729920.
21. *Tang C, Hu Y, Zhang Z, Wei Z, Wang H, Geng Q,* et al. Dexmedetomidine with sufentanil in intravenous patient-controlled analgesia for relief from postoperative pain, inflammation and delirium after esophageal cancer surgery. Biosci Rep 2020; 40(5): BSR20193410.
22. *Bamford NJ, Harris PA, Bailey SR.* Circannual variation in plasma adrenocorticotropic hormone concentrations and dexamethasone suppression test results in Standardbred horses, Andalusian horses and mixed-breed ponies. Aust Vet J 2020; 98(12): 616–21.
23. *Yabeyu AB, Haile KT, Belay YB, Tegegn HG.* Limited Public Knowledge of Chronic Kidney Disease in a Resource-Limited Setting: A Cross-Sectional Study. Int J Gen Med 2022; 15: 4997–5003.
24. *Adeyomoye OI, Akintayo CO, Omotuyi KP, Adewumi AN.* The biological roles of urea: A review of preclinical studies. Indian J Nephrol 2022; 32(6): 539–45.
25. *Nwogueze BC, Ofili IM, Nnama TN, Aloamaka CP.* Oxidative stress-induced by different stressors alters kidney tissue antioxidant markers and levels of creatinine and urea: the fate of renal membrane integrity. Sci Rep 2023; 13(1): 13309.
26. *Viderman D, Tapinova K, Nabidollayeva F, Tankacheev R, Abdildin YG.* Intravenous versus Epidural Routes of Patient-Controlled Analgesia in Abdominal Surgery: Systematic Review with Meta-Analysis. J Clin Med 2022; 11(9): 2579.
27. *Su P, Li Z, Jia X, Peng X, Liu D, Xiao J,* et al. A Response Surface Analysis of the Combination of Dexmedetomidine and Sufentanil for Attenuating the Haemodynamic Response to Endotracheal Intubation. Dose Response 2022; 20(2): 15593258221092367.

Received on November 3, 2023
Revised on February 16, 2024
Revised on March 21, 2024
Revised on May 26, 2024
Accepted on May 28, 2024
Online First July 2024