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SCIENTIFIC ARTICLE

Impact of post-thoracotomy analgesia with dexmedetomidine and morphine on immunocytes: a randomized clinical trial

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KEYWORDS
Thoracotomy;
Dexmedetomidine;
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Abstract
Objective: This study aimed to investigate the impact of post-thoracotomy analgesia with dexmedetomidine and morphine on immunocytes.
Methods: A total of 118 patients with post-thoracotomy Patient-Controlled Intravenous Analgesia (PCIA) in our hospital from March 2016 to July 2018 were randomly selected and divided into the Composite (COM) Group (57 patients administered with dexmedetomidine [1.0 $\mu g.kg^{-1}$ body weight] and morphine [0.48 $mg.kg^{-1}$ body weight]) and the Morphine (MOR) group (61 patients administered with morphine [0.48 $mg.kg^{-1}$]). The values of lymphocyte subsets (CD3+, CD4+, and CD8+) and Natural Killer cells in the peripheral blood of these two groups were detected by FACSCalibur flow cytometry at different time points (before anesthesia induction [T0], immediately after tracheal extubation [T1], 12 hours after surgery [T2], 24 hours after surgery [T3], 48 hours after surgery [T4], 72 hours after surgery [T5], and 7 days after surgery [T6]). The doses of morphine at T3 to T5 and the adverse reactions between the two groups were also recorded and compared.
Results: The CD3+ level and the CD4+/CD8+ ratio at T2 to T5 and the CD4+ level and NK cells at T3 to T5 were significantly higher in the COM Group than in the MOR Group ($p< 0.05$). The postoperative morphine dose and the incidence of postoperative itching, nausea, and vomiting were significantly lower in the COM Group than in the MOR Group ($p< 0.05$).
Conclusions: Dexmedetomidine combined with morphine for post-thoracotomy PCIA can improve the function of immunocytes, reduce morphine consumption, and reduce the adverse reactions during analgesia induction.

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PALAVRAS-CHAVE
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Impacto da analgesia pós-toracotomia com dexmedetomidina e morfina em imunócitos: estudo randomizado

Resumo
Objetivo: Estudar o impacto em linfócitos causado pelo uso da dexmedetomidina associada à morfina para analgesia pós-toracotomia.
Método: Um total de 118 pacientes utilizando Analgesia Intravenosa Controlada pelo Paciente (AICP) pós-toracotomia em nosso hospital de Março de 2016 a Julho de 2018 foram selecionados aleatoriamente e divididos em dois grupos: o Grupo Gombinado [COM, 57 pacientes que receberam dexmedetomidina (1,0 $\mu g.kg^{-1}$ de peso corpóreo) associada à morfina (0,48 $mg.kg^{-1}$ de peso corpóreo)] e o Grupo Morfina [MOR, 61 pacientes, que receberam somente morfina (0,48 $mg.kg^{-1}$)]. Os valores dos subconjuntos de linfócitos (CD3+, CD4+ e CD8+) e das células NK no sangue periférico desses dois grupos foram medidos por citometria de fluxo FACSCalibur em diferentes momentos do estudo [antes da indução anestésica (T0), imediatamente após extubação traqueal (T1), 12 horas após a cirurgia (T2), 24 horas após a cirurgia (T3), 48 horas após a cirurgia (T4), 72 horas após a cirurgia (T5) e 7 dias após a cirurgia (T6)]. As doses de morfina do momento T3 ao T5 e as reações adversas entre os dois grupos também foram registradas e comparadas.
Resultados: O nível de CD3+ e a razão CD4+/CD8+ de T2 a T5, e o nível de CD4+ e as células NK de T3 a T5 do Grupo COM foram significantemente maiores ($p < 0,05$), quando comparados ao Grupo MOR. A dose de morfina no pós-operatório e a incidência de prurido, náusea e vômito no pós-operatório foram significantemente menores no grupo MOR ($p < 0,05$).
Conclusões: Dexmedetomidina combinada com morfina para AICP no período pós-toracotomia pode melhorar a função dos linfócitos, reduzir o consumo de morfina e diminuir reações adversas durante a analgesia.

Introduction

Patients undergoing thoracotomy frequently experience severe pain after surgery, which leads to the inhibition of immune function, specifically cellular immunity, resulting in a bad prognosis.[1,2] Clinically, to alleviate severe pain after thoracotomy, opioid analgesics, such as morphine, are often used for their analgesic effects.[3] However, evidence based on some experimental studies suggests that morphine may inhibit the cellular immunity of the body, thereby possibly promoting the growth and metastasis of residual tumor cells.[4]

As a specific α2-adrenergic receptor agonist, dexmedetomidine can effectively reduce the early body stress and inflammatory response in patients after surgery[5] and alleviate the immunosuppressive effects caused by opioids.[6] Studies have shown[7,8] that dexmedetomidine combined with morphine for non-thoracic surgery can effectively reduce morphine consumption by 20%–30%.

This study attempted to use dexmedetomidine-morphine Patient-Controlled Intravenous Analgesia (PCIA) as postoperative analgesia in patients after thoracotomy, aiming to investigate its impact on postoperative immune function.

Methods

General information

This was a randomized clinical study conducted in Shenzhen People's Hospital from March 2016 to July 2018. It was approved by the hospital's ethics committee. All the patients and their families provided the informed consent.

Patients with the following characteristics were included in the study: 1) Patients with intrathoracic tumors requiring thoracotomy, 2) Patients with the American Society of Anesthesiologists physical status score of I or II, 3) Patients aged between 18 and 80 years, and 4) Patients who were not treated with radiotherapy or chemotherapy 14 days before surgery. However, patients with the following characteristics were excluded: 1) Patients experiencing major bleeding after surgery, 2) Patients requiring a large amount of allogeneic blood infusion, 3) Patients experiencing allergic reactions, and (4) patients with serious organ dysfunction, serious infection, or history of immune system diseases and endocrine system diseases.

All the patients were randomized into the following groups: the composite (COM) Group (dexmedetomi-

dine + morphine) and the morphine (MOR) Group (only morphine) using a random number table.

Method of anesthesia

The two groups were restricted from eating, drinking, and taking medicines 8 hours before surgery. After each patient was sent into the surgery room, the venous access was established for the routine monitoring of the patient's blood pressure, heart rate, electrocardiogram, and arterial blood gas.

Regarding anesthesia induction, 0.05 $mg.kg^{-1}$ midazolam (Roche, Shanghai, China), 0.4 $\mu g.kg^{-1}$ sufentanil (EuroCept Bv, Ankeveen, Netherlands), and 0.2 $mg.kg^{-1}$ cisatracurium (Hengrui Pharma, Lianyungang, China) were intravenously injected, and the Target-Controlled Infusion (TCI) of propofol (Fresenius, Bad Homburg, Germany) was followed to maintain a plasma target concentration of 3 $\mu g.mL^{-1}$. Each patient subsequently underwent tracheal catheterization for mechanical ventilation (frequency, 11–14 times/min; tidal volume, 7–9 $mL.kg^{-1}$; and suction ratio, 1:2).

Regarding anesthesia maintenance, the TCI of propofol with a plasma target concentration of 2–3 $\mu g.mL^{-1}$ and intravenous infusion of 0.5 $\mu g.kg^{-1}.h^{-1}$ sufentanil and 2 $\mu g.kg^{-1}.min^{-1}$ cisatracurium were performed. Each patient's auditory evoked potential index was monitored using one A-line noninvasive anesthesia depth detector (Danmeter Ltd., Odense, Denmark) to maintain an AAI of 10–20.

After the successful completion of surgery, postoperative palinesthesia, and tracheal extubation, PCIA was induced in each patient.

Patient-controlled intravenous analgesia regimens

The patients in the COM group were administered with 150 mL of solution containing 1.0 $\mu g.kg^{-1}$ dexmedetomidine (Hengrui Pharma, Lianyungang, China) and 0.48 $mg.kg^{-1}$ morphine (Northeast Pharmacy, Shenyang, China); the patients in the MOR group were administered with 150 mL of solution containing 0.48 $mg.kg^{-1}$ morphine. The pump parameters were as follows: load, 2 mL; background infusion rate, 2 $mL.h^{-1}$; additional volume, 0.5 mL; locking time, 15 minutes; and maintaining postoperative pain visual analog score, $\leq$ 3 points. For patients with hypotension, Ramsay sedation score > 3, bradycardia, or respiratory rate < 8 beats/min, timely symptomatic treatment should be performed.

Outcomes

A 5 mL of peripheral venous blood was collected from each patient at different time points (before anesthesia induction [T0], immediately after tracheal extubation [T1], 12 hours after surgery [T2], 24 hours after surgery [T3], 48 hours after surgery [T4], 72 hours after surgery [T5], and 7 days after surgery [T6]). The contents of CD3+, CD4+, and CD8+ and Natural Killer (NK) cells in the peripheral blood were detected by FACSCalibur flow cytometry (BD, USA); the CD4+/CD8+ ratio was simultaneously calculated. The doses of morphine at T3 to T5 were recorded separately, and the adverse reactions of the two groups were compared.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 21.0 statistical software. The measurement data were expressed as mean $\pm$ Standard Deviation ($\dot{x} \pm \dot{s}$) The *t*-test was used for the intergroup comparison. The data at different time points were compared using the repeated measurement design analysis of variance. The count data were expressed as the ratio, and the chi-squared test was used for the intergroup comparison.

Results

General conditions

A total of 118 patients (53 men and 59 women) who underwent thoracotomy in our hospital were included in this study. Their ages ranged from 41 to 60 years, and they weighed 49–65 kg, with a Body Mass Index (BMI) of 19–23 $kg.m^{-2}$. A total of 65 patients had esophageal cancer, 21 had gastric cardia cancer, and 16 had mediastinal tumor, and 16 patients previously underwent the partial resection of the lung tumor. The COM Group was composed of 57 patients (29 men and 28 women) aged 52.2 $\pm$ 6.9 years and weighing 57.2 $\pm$ 3.9 kg. The MOR group consisted of 61 patients (27 men and 34 women) aged 52.9 $\pm$ 7.4 years and weighing 57.9 $\pm$ 4.5 kg. There were no significant differences in the sex composition, age, body weight, or BMI between the two groups (Table 1).

Morphine consumption

The morphine consumption in the COM Group at T3 to T5 was significantly lower than that in the MOR Group ($p < 0.05$) (Table 2).

Levels of CD3+, CD4+, CD8+, and natural killer cells in the peripheral blood

Compared with the contents at T0, the contents of CD3+, CD4+, CD4+/CD8+, and NK cells were significantly lower at T1 to T5 in both groups ($p < 0.05$), while there were no significant differences in the contents of CD3+, CD4+, CD4+/CD8+, and NK cells at T6. The CD3+ level and CD4+/CD8+ ratio at T2 to T5 and the CD4+ level and NK cells at T3 to T5 in the COM group were significantly higher than those in the MOR Group ($p < 0.05$). There were no significant differences in CD3+, CD4+, CD4+/CD8+, and NK cells between the COM Group and the MOR Group at T6 (Table 3).

Adverse reactions

The incidence of postoperative pruritus, nausea, and vomiting in the COM group was significantly lower than that of the MOR Group ($p < 0.05$) (Table 4). Complications such as

Table 1 Comparison of general conditions of the two groups.

Group	n	M/F (n)	Age (years)	Weight (kg)	BMI (kg. m^{-2})
COM	57	29/28	52.2 ± 6.9	57.2 ± 3.9	21.7 ± 1.6
MOR	61	27/34	52.9 ± 7.4	57.9 ± 4.5	21.2 ± 1.1

Table 2 Comparison of postoperative morphine consumption of the two groups [(ẋ±ṡ) mg].

Group	n	T3	T4	T5
COM	57	16.5 ± 6.7[a]	35.8 ± 9.7[a]	55.3 ± 8.9[a]
MOR	61	27.6 ± 9.5	51.9 ± 11.2	73.2 ± 7.6

Note: Compared with group MOR, [a] $p < 0.05$.

Table 3 Changes of lymphocyte subsets and NK cells in peripheral blood in different groups at different time points (ẋ±ṡ).

Index	Group	n	T_0	T_1	T_2	T_3	T_4	T_5	T_6
$CD3^+$ (%)	COM	57	63.1 ± 4.5	57.1 ± 3.7[a]	54.9 ± 3.4[ab]	52.7 ± 2.7[ab]	57.3 ± 4.1[ab]	59.7 ± 5.1[ab]	62.8 ± 4.2
	MOR	61	62.8 ± 4.7	55.3 ± 4.1[a]	52.6 ± 3.6[a]	49.7 ± 4.3[a]	53.6 ± 3.7[a]	57.5 ± 2.4[a]	62.3 ± 4.5
$CD4^+$ (%)	COM	57	36.9 ± 4.5	31.7 ± 1.9[a]	29.5 ± 2.2[a]	28.2 ± 2.9[ab]	31.5 ± 4.3[ab]	32.9 ± 5.4[ab]	35.6 ± 4.0
	MOR	61	36.5 ± 4.2	31.9 ± 5.7[a]	27.1 ± 2.9[a]	24.8 ± 3.1[a]	27.3 ± 5.2[a]	29.8 ± 3.6[a]	33.5 ± 3.7
$CD8^+$ (%)	COM	57	24.3 ± 4.4	23.8 ± 4.5	23.2 ± 4.3	22.9 ± 4.2	23.5 ± 3.9	24.1 ± 4.1	23.9 ± 4.3
	MOR	61	24.7 ± 4.6	24.3 ± 4.5	24.0 ± 4.2	23.9 ± 4.4	24.1 ± 3.9	23.7 ± 3.7	24.3 ± 4.1
$CD4^+$/ $CD8^+$	COM	57	1.5 ± 0.3	1.2 ± 0.2[a]	1.2 ± 0.2[ab]	1.2 ± 0.2[ab]	1.3 ± 0.2[ab]	1.4 ± 0.1[ab]	1.5 ± 0.3
	MOR	61	1.5 ± 0.2	1.2 ± 0.3[a]	1.1 ± 0.2[a]	1.1 ± 0.3[a]	1.2 ± 0.1[a]	1.3 ± 0.2[a]	1.4 ± 0.2
NK cells (%)	COM	57	14.4 ± 1.9	12.1 ± 1.2[a]	11.8 ± 1.5[a]	11.4 ± 1.4[ab]	13.1 ± 1.3[ab]	13.5 ± 1.6[ab]	14.2 ± 1.7
	MOR	61	14.6 ± 2.2	11.9 ± 1.6[a]	11.1 ± 1.2[a]	10.3 ± 1.8[a]	11.6 ± 1.5[a]	12.9 ± 1.4[a]	14.2 ± 2.0

Note: Compared with T0, [a] $p < 0.05$; compared with group MOR, [b] $p < 0.05$.

Table 4 Postoperative adverse reactions in the two groups, n (%).

Group	n	Pruritus	Nausea	Vomiting
COM	57	3 (5.3)[a]	9 (15.8)[a]	6 (10.5)[a]
MOR	61	13 (21.3)	23 (37.7)	15 (24.6)

Note: Compared with group MOR, [a] $p < 0.05$.

hypotension, bradycardia, or excessive sedation were not observed in both groups.

Discussion

Considering the significant damage to the muscles, fascia, and other tissues, thoracotomy frequently causes more severe pain than other surgeries. Additionally, thoracotomy will affect breathing, cough, and expectoration, cause a difficulty in the discharge of respiratory secretions, and result in complications such as atelectasis, pulmonary infection, or chest infection.[9]

Although opioid analgesics have good analgesic effects after thoracotomy, they can also lead to adverse reactions.[10] Some studies[11,12] have pointed out that postoperative analgesia methods and occurrence of postoperative complications have a certain correlation. As a common postoperative analgesia method, PCIA can maintain a relatively stable blood concentration, thus avoiding the mismatch between blood concentration and analgesia, reducing the amount of analgesic medication, and subsequently obtaining better analgesic effects.[13,14]

In this study, all the subjects were treated with PCIA. This study referred to relevant research reports[15,16] and used dexmedetomidine + morphine for postoperative analgesia, and the results showed that the morphine consumption in the COM Group at T3 to T5 was lower than that in the MOR Group. Moreover, the incidence of postoperative pruritus, nausea, and vomiting was also lower in the COM group than in the MOR Group, and complications such as hypotension, bradycardia, or excessive sedation were not observed in both groups, indicating that dexmedetomidine combined with morphine in PCIA can effectively reduce morphine consumption and postoperative complications and cause less postoperative complications, suggesting that the dosage and administration of dexmedetomidine are considered safe and effective.

The T lymphocyte subsets play an important role in maintaining the stability of the immune system.[17] CD3+ is an important subset of T lymphocytes, and its number can directly reflect the level of mature T-cells in the peripheral

blood. CD4+ lymphocyte subsets are an important helper of T lymphocytes, which can help the body resist foreign microorganisms and tumor cells. CD8+ lymphocytes can inhibit the immune regulation function of the body. The stable ratio of CD4+ to CD8+ is important for maintaining the normal immune function of the body. Simultaneously, CD4+/CD8+ can also be used as an indicator of the severity and prognosis of diseases.[18] The number of NK cells is important for the body's antitumor immunity, which can directly kill tumor cells. When the in vivo cellular immune function is inhibited, the number will significantly reduce.[19] The results of this study showed that compared with the contents at T0, the contents of CD3+, CD4+, CD4+/CD8+ and NK cells were lower at T1 to T5, which may be related to the oxidative stress induced by thoracotomy wounds and the immune function inhibition by morphine.[20] This study showed that the CD3+ level and the CD4+/CD8+ were higher in the COM group at T2 to T5 than those in the MOR group, and the contents of CD4+ and NK cells at T3 to T5 were also higher in the COM group than those in the MOR group, indicating that dexmedetomidine can effectively reduce the inhibition of cellular immunity caused by morphine analgesia after thoracotomy.

In recent years, some studies have reported the potential benefits of dexmedetomidine for postoperative analgesia and its positive effects on immune system. Lin et al.[21] suggested that the addition of dexmedetomidine to intravenous patient-controlled analgesia morphine resulted in superior analgesia, significant morphine sparing, and less morphine-induced nausea, preventing additional sedation and untoward hemodynamic changes. Cai et al.[22] reported that DEX may enhance the immune function of rats with ovarian cancer by inhibiting the p38MAPK/NF-κB signaling pathway. Ma et al.[23] indicated that the combined use of dexmedetomidine and flurbiprofen axetil significantly improved pain after general anesthesia thyroid surgery, reduced restlessness and postoperative cognitive dysfunction, enhanced immune function, and promoted wound repair. Dong et al.[24] confirmed that dexmedetomidine can effectively reduce the release of inflammatory factors in patients who underwent the radical resection of gastric cancer, and the anti-inflammatory effect may be enhance by downregulating the expression of NF-κB. Moreover, dexmedetomidine can also alleviate the reduction in the subgroups of CD3+ and CD4+, thereby ameliorating the impaired immune functions.

Limitations

This study is only limited to patients below 60 years-old. Whether this combination can be effective for patients over 60 years-old, as well as combining with chronic diseases or vital organ dysfunction, and whether it will have impact on the prognosis of patients still require further research and confirmation.

Conclusion

In summary, dexmedetomidine-morphine PCIA for post-thoracotomy analgesia can effectively reduce morphine consumption, reduce the occurrence of adverse reactions during analgesia and improve the cellular immune function of patients.

Conflicts of interest

The authors declare no conflicts of interest.

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