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Original Article

Effect of postoperative hydrocodone analgesia on inflammatory factors, NSE levels, and cognitive function in elderly patients undergoing hip arthroplasty

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Abstract: Aims: To explore the effect of postoperative hydrocodone analgesia on inflammatory factors, NSE levels, and cognitive function in elderly patients undergoing hip arthroplasty. Methods: A retrospective analysis was conducted on elderly patients undergoing hip arthroplasty from January 2020 to December 2023. Among them, 43 patients with postoperative hydrocodone analgesia were included in an observation group, and 57 patients without postoperative hydrocodone analgesia in a control group. We compared the differences of general clinical data, inflammatory factors (CRP, WBC and PCT), NSE levels, and cognitive function. Results: After surgery, the VAS scores decreased in both groups compared to before treatment, and the decrease was more significant in the observation group than the control group ($P < 0.05$). The NSE, WBC, CRP, and PCT level in the control group were significantly higher than those in the observation group at one day, 3 days, and 7 days after surgery ($P < 0.05$). Moreover, the MMSE score and the serum S100β protein concentration significantly improved in the observation group at one day, 3 days and 7 days after surgery compared to the control group ($P < 0.05$). Conclusion: Postoperative hydrocodone analgesia can reduce the release of inflammatory factors after elderly hip replacement surgery, alleviating postoperative pain, and reducing the incidence of early postoperative cognitive impairment.

Keywords: Postoperative hydrocodone analgesia, inflammatory factors, NSE levels, cognitive function, elderly patients, hip arthroplasty

Introduction

With the growing issue of population aging, hip fractures, avascular necrosis of the femoral head, osteoarthritis, and other hip joint conditions have become increasingly prevalent among the elderly [1, 2]. These conditions, characterized by high rates of injury and disability, significantly impact the physical and mental well-being of older adults, as well as their overall quality of life [3]. Currently, hip joint replacement surgery is the primary treatment for hip joint diseases [4]. However, during the procedure, traction injury to the skin and ligaments, excision of the joint capsule and femoral head, and expansion of the marrow cavity can damage nerve endings. This damage can cause the cells to secrete inflammatory factors, leading to pain stress, increased neuronal sensitivity, and a lowered pain threshold. As a result, patients may experience heightened nociceptive pain, which can negatively affect the postoperative recovery of elderly patients [5].

Research has shown that effective perioperative pain management can mitigate stress, reduce inflammatory responses, and prevent postoperative cognitive dysfunction, thereby improving patient outcomes [6-8]. Currently, multimodal analgesia is widely used for pain management following hip replacement surgery, offering effective pain relief and reducing complications, which helps accelerate postoperative recovery. While intravenous analgesia is easy to administer, it has limited effectiveness in controlling movement-related pain and is associated with adverse effects such as postoperative nausea and vomiting, urinary reten-

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tion, respiratory depression, and sedation. Conversely, epidural analgesia carries risks including epidural hematoma, spinal cord nerve damage, and infection. Its clinical application is further limited by the routine use of anticoagulants after hip replacement surgery [9, 10]. Therefore, selecting the appropriate postoperative pain management strategy for elderly patients undergoing hip replacement surgery is particularly crucial.

Hydrocodone hydrochloride is a novel semi-synthetic opioid, derived from morphine, acting as an agonist of the μ-opioid receptor. When administered intravenously, it has an onset time of 15 minutes, reaches peak effect within 15 to 30 minutes, and has a duration of action of approximately 2-3 hours. Its analgesic effect is about 1/8 to 1/5 that of morphine, but its potency is 8 to 10 times greater [11, 12]. Hydrocodone hydrochloride is known for its rapid onset, strong analgesic effects, inactive metabolites, and fewer adverse reactions, making it widely used in clinical anesthesia and postoperative pain management [13]. However, the full extent of its efficacy, potency, and other pharmacological properties is not yet completely understood. There were also significant variations in the reported efficacy and side effects at different concentrations [14, 15]. Currently, research on the use of hydrocodone hydrochloride for postoperative pain management is limited, as is research on its effects on postoperative cognitive function and inflammatory response.

Therefore, this study aims to evaluate the postoperative analgesic effect of hydrocodone hydrochloride in elderly patients undergoing hip arthroplasty. Specifically, we assessed postoperative pain relief (Visual Analogue Scale (VAS) score), inflammatory response, NSE levels, postoperative recovery, postoperative adverse reactions, and postoperative cognitive dysfunction (S100β protein, Mini-Mental State Examination (MMSE) score). The findings of this study are intended to provide valuable insights for the rational and safe clinical application of hydrocodone hydrochloride.

Methods and participants

Clinical data

A total of 100 elderly patients who underwent hip arthroplasty between January 2020 and December 2023 were recruited. Among them, 43 patients with postoperative hydrocodone analgesia were classified as the observation group, while 57 patients without were classified as the control group.

This study was approved by the Ethics Committee of The First Affiliated Hospital of Nanchang University, and signed informed consent was obtained from the patients.

Inclusion criteria for the observation group

Patients underwent unilateral hip arthroplasty under general anesthesia, were classified as ASA I-II, aged 65 to 80 years, experienced pain that impacted rest and rehabilitation exercises, had a VAS score of more than 4, had normal liver and kidney function, and were users of hydrocodone.

Inclusion criteria for the control group

Patients underwent unilateral hip arthroplasty under general anesthesia, were classified as ASA I-II, aged 65 to 80 years, experienced pain that affected rest, rehabilitation exercises, and other activities, had a VAS score of more than 4, received sufentanil for pain management, and had normal liver and kidney function.

Exclusion criteria

Exclusion criteria included patients allergic to hydrocodone; patients with a history of craniocerebral trauma, epilepsy, or cerebrovascular disease; patients unable to cooperate with cognitive function evaluations; patients with cardiopulmonary insufficiency; patients with malignant tumors; patients with mental disorders affecting cognition; patients who were pregnant or breastfeeding; patients with gastrointestinal or urinary tract hemorrhage; patients unable to complete the MMSE within 30 minutes at admission.

Methods

The patients were positioned supine, and a 16-gauge indwelling needle was used to establish a venous channel for infusion of compound sodium chloride at a rate of 20 ml/kg/h. Monitoring included electrocardiogram, non-invasive blood pressure cuff, pulse oximetry, and end-tidal carbon dioxide pressure. All patients received total intravenous anesthesia.

For induction of anesthesia, patients in the control group received an intravenous injection of sufentanil (H20054172, Yichang Renfu Pharmaceutical Co., Ltd.) at 0.5 μg/kg, while those in the observation group received hydrocodone (H20046493, Jiangsu Yabang Qiangsheng Pharmaceutical Co., Ltd.) at 0.02 mg/kg. This was followed by intravenous injections of midazolam (0.05 mg/kg), etomidate (0.4 mg/kg), and cisatracurium (0.15 mg/kg). Mechanical ventilation with oxygen was initiated, and anesthesia was maintained with propofol (6 $mg \cdot kg^{-1} \cdot h^{-1}$) and remifentanil (0.6 $\mu g \cdot kg^{-1} \cdot h^{-1}$). Before the end of surgery, both groups received an intravenous injection of rocuronium (2 mg) for skin closure and were connected to a portable infusion pump. The control group received an infusion of sufentanil (2 μg/kg) combined with normal saline to a total volume of 100 mL, while the observation group received an infusion of hydrocodone (0.02 mg/kg) with normal saline to a total volume of 100 mL. Both infusions were administered at a flow rate of 2 mL/h, with a patient-controlled dose of 0.5 mL and a lockout interval of 15 minutes.

After surgery, patients were returned to the ward once fully awake. All patients received a postoperative intravenous patient-controlled analgesia pump with the same drug dosage and flow rate as described above.

Pain was assessed using the VAS [16], where a higher VAS score indicates more significant pain.

Cognitive function was evaluated using the MMSE [17]. The MMSE assesses 7 dimensions: orientation to time, orientation to place, immediate memory, attention and calculation, delayed memory, language, and visuospatial abilities. A lower MMSE score indicates more severe cognitive impairment.

Detection indicators

Using EDTA-K2 anticoagulant vacuum blood collection tubes, blood samples (5 mL) were drawn from the cubital vein of patients at 4 time points: before anesthesia, 1 hour after surgery, 6 hours after surgery, and 24 hours after surgery. The collected samples were labeled, and stored in a refrigerator at 4°C. Then, they were promptly centrifuged at 4000 rpm for 10 minutes, and the serum was stored at -70°C. Following specimen collection, the concentrations of WBC, CRP, PCT, S100β, brain-derived neurotrophic factor (BDNF), neurofilament light chain (NFL), and neuron-specific enolase (NSE) levels in the serum were measured using ELISA. The detection followed the operational procedures of the corresponding kits: WBC (Wuhan Yipu Biotechnology Co., Ltd., Cat. No. CK-E10083), CRP (Shanghai Guduo Biotechnology Co., Ltd., Cat. No. GD-S0135-B), PCT (Chuzhou Shinuoda Biological Technology Co., Ltd., Cat. No. SND-H1925), S100B (Guangzhou Juyan Biotechnology Co., Ltd., Cat. No. ELH-S100B-2), and NSE (Guangzhou Yuwei Biotechnology Instrument Co., Ltd., Cat. No. GK-E0275H).

Statistical analysis

The experimental data were analyzed using SPSS 20.0 statistical software. Quantitative data are presented as mean ± standard deviation ($\bar{x} \pm s$). For comparisons between groups at the same time point, an independent sample t-test was used if the data followed a normal distribution. If the data did not follow a normal distribution, the Wilcoxon rank-sum test was employed. Categorical data are presented as number (percentage), and group comparisons were conducted using the Chi-square test. A *p*-value of < 0.05 was considered statistically significant.

Results

The baseline demographic and clinical characteristics are detailed in **Table 1**. The mean age of the control group was 76.23±10.06 years, while the observation group had a mean age of 74.56±9.56 years. There were no significant differences between the two groups in terms of BMI, gender, occupation, economic income, and medical history ($P > 0.05$). Perioperative indicators, including operation time, bleeding volume, blood transfusion volume, and hospitalization time, were also assessed. The results indicated no significant differences between the two groups in these perioperative measures ($P > 0.05$) (**Table 2**).

One day before surgery, the VAS score in the observation group was 8.1±0.8 points, while in the control group, it was 8.0±0.6 points. One, three, and seven days after surgery, VAS scores

Table 1. Comparison of clinical characteristics between the two groups

	Control group (n=57)	Observation group (n=43)	χ^2	P
Age	76.23±10.06	74.56±9.56	0.387	0.687
BMI	21.93±2.34	22.46±2.67	1.297	0.227
Gender			0.985	0.354
Male	25 (43.86%)	23 (53.49%)		
Female	32 (56.14%)	20 (46.51%)		
Marital status			1.356	0.756
Unmarried	4 (7.02%)	1 (2.33%)		
Married	28 (49.12%)	27 (62.79%)		
Divorced	1 (1.75%)	2 (4.65%)		
Widowed	24 (42.11%)	13 (30.23%)		
Employment status			2.567	0.267
Employed	4 (7.02%)	4 (9.30%)		
Retired	28 (49.12%)	27 (62.79%)		
Unemployed	25 (43.86%)	12 (27.91%)		
Educational level			2.574	0.274
Below primary school	25 (43.86%)	20 (46.51%)		
Middle school	31 (54.39%)	21 (48.84%)		
University	1 (1.75%)	2 (4.65%)		
Medical expense			5.373	0.078
Self-funded	17 (29.82%)	10 (23.26%)		
Public expenses	11 (19.30%)	10 (23.26%)		
Medical insurance	29 (50.88%)	23 (53.48%)		
Income			0.378	0.847
< 2000	15 (26.32%)	15 (34.88%)		
2000-10000	24 (42.11%)	21 (48.84%)		
> 10000	18 (31.57%)	7 (16.28%)		
Previous surgical history			0.013	0.941
Yes	5 (8.77%)	6 (13.95%)		
No	52 (91.23%)	37 (86.05%)		
Previous hypertension			0.197	0.641
Yes	11 (19.30%)	11 (25.58%)		
No	46 (80.70%)	32 (74.42%)		
Previous heart disease			0.946	0.334
Yes	5 (8.77%)	3 (6.98%)		
No	52 (91.23%)	40 (93.02%)		
Previous diabetes			1.927	0.174
Yes	6 (10.53%)	4 (9.30%)		
No	51 (89.47%)	39 (90.70%)		
Previous tumor history			0.924	0.338
Yes	1 (1.75%)	2 (4.65%)		
No	56 (98.25%)	41 (95.35%)		
Surgical type			1.746	0.187
Half hip	27 (47.37%)	23 (53.49%)		
Total hip	30 (52.63%)	20 (46.51%)		

decreased in both groups compared to pre-treatment, with the observation group showing significantly lower scores than the control group ($P < 0.05$) (**Figure 1**). The NSE levels in both

Table 2. Comparison of perioperative indicators between the two groups

	Control group (n=57)	Observation group (n=43)	t	p
Operation time	3.26±0.74	3.25±0.84	0.336	0.746
Intraoperative bleeding volume	564.98±184.67	523.64±223.37	0.997	0.246
Intraoperative blood transfusion volume	0.74±0.97	0.64±1.25	0.387	0.697
Length of hospital stay	7.45±1.87	6.98±1.27	0.287	0.739

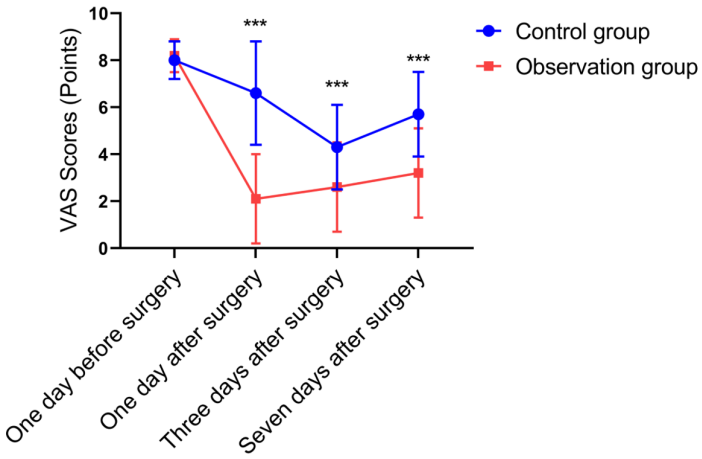

Figure 1. Comparison of VAS scores between two groups. ***P < 0.001, compared to the control group.

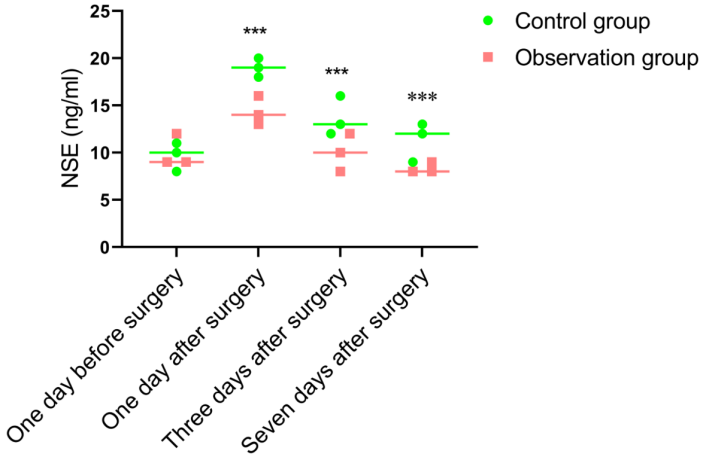

Figure 2. Comparison of NSE concentrations between the two groups. ***P < 0.001, compared to the control group.

groups were significantly elevated one day after the operation. Additionally, the NSE level in the control group was significantly higher than that in the observation group at one day, three days, and seven days post-surgery (P < 0.05) (**Figure 2**). WBC, CRP, and PCT levels were significantly increased one day after the operation in both groups. Furthermore, the WBC and CRP levels in the control group were significantly higher than those in the observation group at one day and three days post-surgery (P < 0.05) (**Figure 3**).

The MMSE score was 25.39±2.74 points in the observation group and 24.84±3.52 points in the control group 1 day before surgery. One day after surgery, the MMSE scores of both groups improved compared to pre-treatment, but the observation group had significantly higher scores than the control group (P < 0.05) (**Table 3**). Additionally, the serum S100β protein concentration was significantly increased in both groups one day after the operation. The S100β protein levels in the control group were notably higher than those in the observation group at one day, three days, and seven days post-surgery (P < 0.05) (**Figure 4**).

A comparison of adverse reactions between the observation and control groups is summarized in **Table 4**. The observation group had a lower incidence of adverse reactions compared to the control group (20.9% vs. 31.6%). The difference in the incidence of adverse reactions was significant between the groups (P=0.011).

The NFL levels were significantly increased after surgery, and the increases were higher in the control group. Additionally, the BDNF levels were significantly decreased after surgery, and the decreases in the control group more significant than those in the observation group at one day, three days, and seven days post-surgery (P < 0.05) (**Figure 5**).

Discussion

The results of this study indicate that the observation group, which used hydrocodone for post-

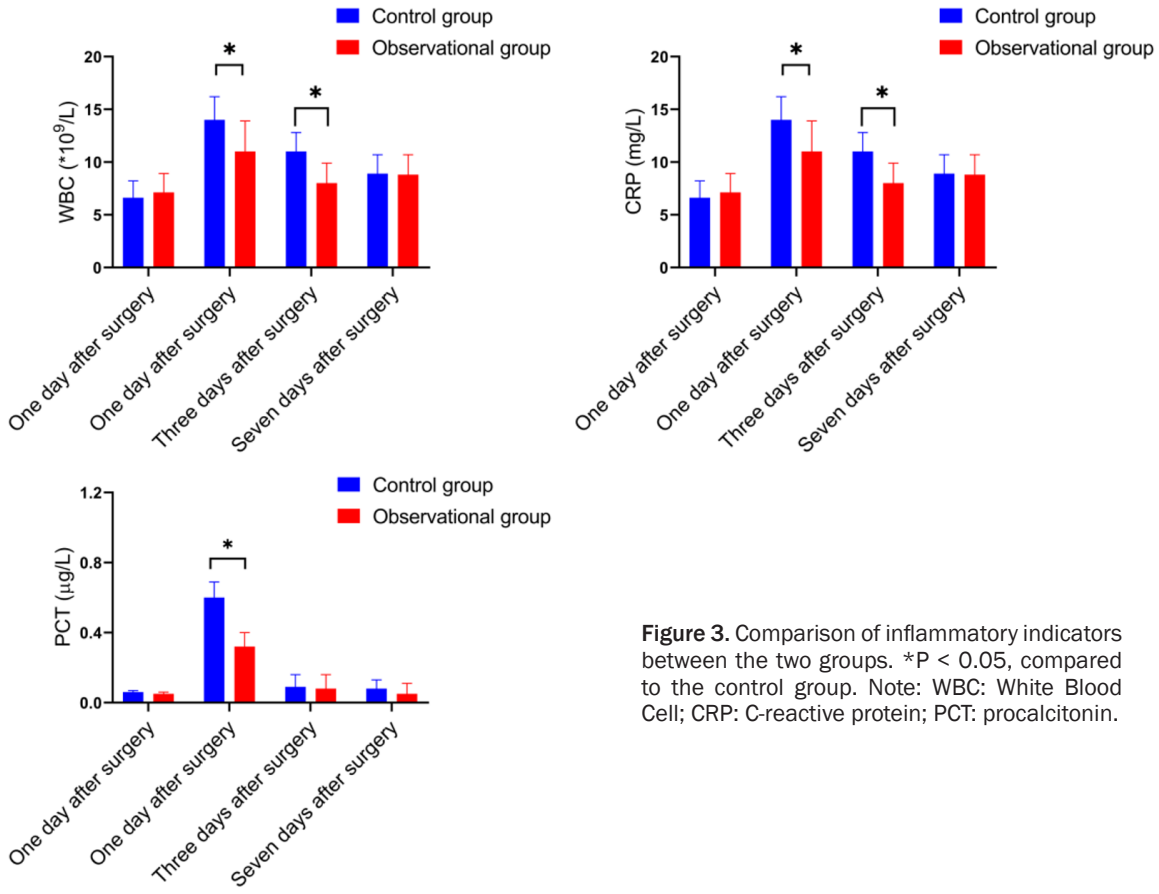

Figure 3. Comparison of inflammatory indicators between the two groups. *P < 0.05, compared to the control group. Note: WBC: White Blood Cell; CRP: C-reactive protein; PCT: procalcitonin.

Table 3. Comparison of MMSE between two the groups

Group	One day before surgery	One day after surgery	Three days after surgery	Seven days after surgery
Control group (n=57)	24.84±3.52	20.52±3.56	24.58±3.37	24.50±3.51
Observation group (n=43)	25.39±2.74	25.42±2.78	25.65±2.47	25.97±2.64
t	0.387	3.497	0.219	0.393
P	0.675	0.012	0.443	0.367

operative patient-controlled intravenous analgesia, had significantly lower VAS scores compared to the control group. Some scholars have suggested that hydrocodone provides effective postoperative patient-controlled analgesia with fewer adverse reactions in elderly patients undergoing hip arthroplasty [18, 19]. In addition, research has shown that hydrocodone offers superior analgesic effects compared to sufentanil in orthopedic postoperative care, with VAS scores in the hydrocodone group being lower than those in the sufentanil group 2 to 48 hours postoperatively [20]. These findings align with the results of this study, demonstrating that hydrocodone has a better analgesic effect following total hip arthroplasty.

Hydrocodone is a highly potent opioid analgesic that delivers effective pain relief even at lower doses. This is particularly important for elderly patients, who may be more sensitive to opioid side effects and therefore require lower doses for adequate pain management. Additionally, hydrocodone has a rapid onset of action, providing quick pain relief immediately after surgery [21]. This rapid relief is crucial in the postoperative period when patients may experience severe pain. Moreover, hydrocodone offers a longer duration of action compared to other opioids, ensuring sustained pain relief over an extended period [22]. This continuous relief is beneficial for elderly patients who may need ongoing pain management in the days following

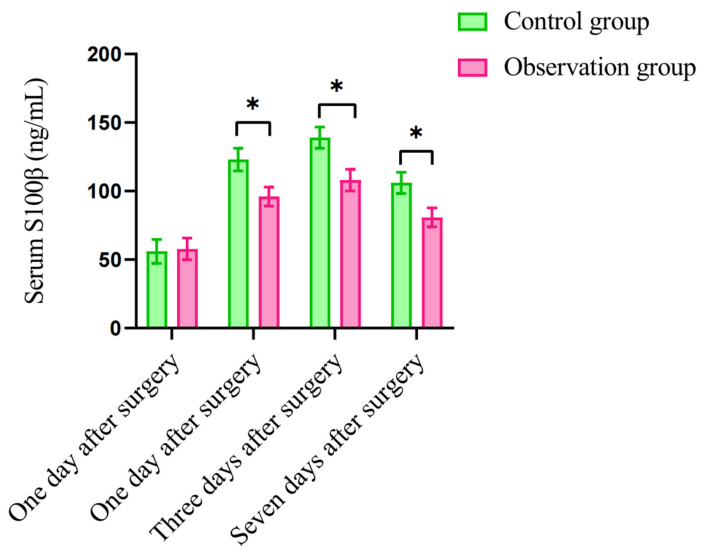

Figure 4. Comparison of serum S100β protein concentration between the two groups. *P < 0.05, compared to the control group.

surgery. Furthermore, hydrocodone is associated with fewer side effects, such as nausea, vomiting, and respiratory depression, compared to other opioids. This reduced incidence of adverse effects is particularly advantageous for elderly patients, who are often more susceptible to the side effects of opioids.

Our study also revealed that postoperative analgesia with hydrocodone effectively reduced levels of inflammatory factors such as PCT, WBC, and CRP in elderly patients undergoing total hip arthroplasty. After total hip replacement surgery, inflammatory factors accumulate in the tissues surrounding the hip joint, stimulating chemical receptors and leading to pain [23]. Additionally, the release of inflammatory cytokines such as IL-1β, IL-6, and IL-8 can enhance the sensitivity of the peripheral nervous system to stimuli [24, 25]. When inflammatory factors are excessively activated and released, they can impact sensory fibers through systemic circulation [26]. This disruption in the normal physiological function of sensory fibers can alter their excitability, affecting the intensity and duration of pain experienced by nociceptors. Clinically, this often results in increased pain perception by the patient. Research has shown [27, 28] that timely interventions to reduce the release of local pain-inducing substances can alleviate pain. Pain management with hydrocodone can improve patient comfort and mobility, facilitating earlier ambulation and rehabilitation [29]. Early mobilization helps prevent complications such as deep vein thrombosis and pneumonia, which are linked to elevated levels of inflammatory markers like WBC and CRP. By promoting early mobilization, hydrocodone indirectly contributes to reducing these inflammatory markers [30].

In this study, there was no significant difference in preoperative MMSE scores between the observation and control groups. However, 24 hours postoperatively, the MMSE scores in the observation group were significantly higher than those in the control group. This improvement may be attributed to more effective postoperative analgesia with hydrocodone, which likely reduced inflammatory responses and other contributing factors. These findings suggest that postoperative hydrocodone analgesia has a positive effect on cognitive function in elderly patients undergoing hip arthroplasty and may reduce the incidence of postoperative cognitive dysfunction. Several factors can influence cognitive changes in elderly patients after surgery, including preoperative mental status, psychological factors, emotional conditions, underlying diseases, anesthesia methods, surgical techniques, duration of surgery, and intraoperative blood loss [31]. Effective pain management with hydrocodone can help mitigate the overall stress response to surgery, including inflammation and pain-induced stress, which are known to contribute to cognitive dysfunction [32]. Hydrocodone's sedative properties can promote relaxation and reduce anxiety, potentially minimizing the risk of delirium and cognitive impairment postoperatively [33]. Elderly patients may require lower doses of hydrocodone compared to younger patients due to age-related changes in drug metabolism and sensitivity. This adjustment can help reduce the risk of opioid-related side effects that might contribute to cognitive dysfunction [34]. Additionally, hydrocodone's ability to modulate the inflammatory response associated with surgery can further protect cognitive function [35]. By reducing inflammation, hydrocodone may help preserve cognitive function in elderly patients. Effective pain management with hydrocodone

Table 4. Comparison of adverse reactions between two the groups

Adverse reactions	Control group (n=57)	Observation group (n=43)	χ^2	P
Awakening restlessness	1	4	11.89	0.009
Nausea and vomiting	12	5	10.27	0.015
Skin itching	1	0		
Respiratory suppression	1	0		
Uroschesis	2	0		
Constipation	1	0		
Total	18 (31.6%)	9 (20.9%)	10.38	0.011

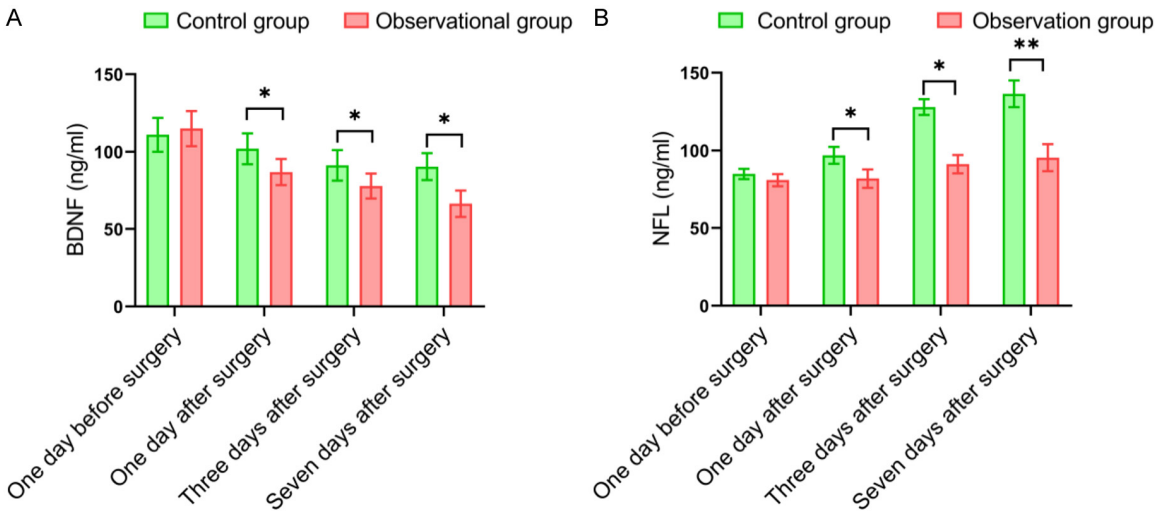

Figure 5. Comparison of serum BDNF and NFL between the two groups. A: Brain-derived neurotrophic factor (BDNF); B: Neurofilament light chain (NFL). *P < 0.05, compared to the control group; **P < 0.01, compared to the control group.

can also facilitate faster recovery and rehabilitation, potentially lowering the overall risk of cognitive dysfunction by encouraging early mobilization and engagement in cognitive activities.

Interestingly, we observed a time-dependent decrease in postoperative serum BDNF levels in the observation group compared to preoperative levels. Several factors may contribute to this phenomenon. First, surgical trauma: The trauma associated with surgery initiates a series of complex physiological and neuroendocrine responses. These responses may interact with the effects of hydrocodone, collectively influencing the time-dependent changes in serum BDNF levels. Second, hydrocodone's effect: As an opioid analgesic, hydrocodone may directly or indirectly influence the synthesis, release, or metabolism of BDNF. This could be due to its impact on neural signal transduction pathways or other mechanisms, leading to specific temporal changes in BDNF content [36]. Third, metabolic state and inflammatory response: During postoperative recovery, changes in the body's overall metabolic state and inflammatory response might also affect BDNF dynamics. Future research is needed to further investigate and clarify these mechanisms, to better understand the relationship between hydrocodone, serum BDNF levels, and their potential clinical significance.

However, this study has certain limitations. Firstly, the sample size is relatively small, which may restrict the statistical power and generalizability of the findings. Secondly, the use of the VAS and MMSE introduces some degree of individual variability and subjectivity, which could influence the results. Lastly, due to limitations in available resources at our hospital, data on additional inflammatory markers were not

included in the analysis. Future research should address these limitations by increasing the sample size and conducting a multicenter, prospective study. This will help further explore the application value of hydrocodone for postoperative analgesia in elderly patients undergoing total hip arthroplasty and provide a more comprehensive understanding of its efficacy and impact.

In summary, postoperative analgesia with hydrocodone effectively reduces levels of postoperative inflammatory factors such as PCT, WBC, and CRP, mitigating the body's inflammatory response. It also lowers the incidence of adverse reactions and cognitive dysfunction associated with postoperative analgesia. Therefore, hydrocodone is a viable option for postoperative pain management in elderly patients undergoing hip replacement surgery.

Disclosure of conflict of interest

None.

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References

[1] Shigemoto K, Sawaguchi T, Higashikawa T and Okuro M. Differences in age-related characteristics among elderly patients with hip fractures. J Orthop Sci 2023; 28: 1131-1135.

[2] Yaacobi E, Shachar T, Segal D, Agabaria A, Halima G, Marom O and Ohana N. Unveiling the economic toll of surgical learning curve in elderly hip fractures. J Clin Med 2023; 12: 4880.

[3] da Silva ARB, Martinez LC, de Medeiros Pinheiro M and Szejnfeld VL. Secular trends in hip fractures in adults over 50 years old: a retrospective analysis of hospital admissions to the Brazilian Public Health System from 2004 to 2013. Arch Osteoporos 2022; 17: 50.

[4] Henkel C, Styrkársdóttir U, Thorleifsson G, Stefánsdóttir L, Björnsdóttir G, Banasik K, Brunak S, Erikstrup C, Dinh KM, Hansen TF, Nielsen KR, Bruun MT, Dowsett J, Brodersen T; DBDS Genomic Consortium, Thorgeirsson TE, Gromov K, Boesen MP, Ullum H, Ostrowski SR, Pedersen OB, Stefánsson K and Troelsen A. Genome-wide association meta-analysis of knee and hip osteoarthritis uncovers genetic differences between patients treated with joint replacement and patients without joint replacement. Ann Rheum Dis 2023; 82: 384-392.

[5] Liu H, Gao M, Zheng Y, Sun C, Lu Q and Shao D. Effects of dexmedetomidine at different dosages on perioperative haemodynamics and postoperative recovery quality in elderly patients undergoing hip replacement surgery under general anaesthesia: a randomized controlled trial. Trials 2023; 24: 386.

[6] Sameer M, Muthu S and Vijayakumar PC. Enhanced recovery after surgery (ERAS) protocol in geriatric hip fractures: an observational study. Cureus 2023; 15: e42073.

[7] Kondylakis H, Chicchi Giglioli IA, Katehakis DG, Aldemir H, Zikas P, Papagiannakis G, Hors-Fraile S, González-Sanz PL, Apostolakis KC, Stephanidis C, Núñez-Benjumea FJ, Baños-Rivera RM, Fernandez-Luque L and Kouroubali A. A digital health intervention for stress and anxiety relief in perioperative care: protocol for a feasibility randomized controlled trial. JMIR Res Protoc 2022; 11: e38536.

[8] Barrington JW, Halaszynski TM and Sinatra RS; Expert Working Group On Anesthesia And Orthopaedics Critical Issues In Hip And Knee Replacement Arthroplasty FT. Perioperative pain management in hip and knee replacement surgery. Am J Orthop (Belle Mead NJ) 2014; 43 Suppl: S1-S16.

[9] Chang JS, Lee DH, Kang MW, Kim JW and Kim CH. Effectiveness of intravenous non-opioid analgesics for postoperative pain management of in patients undergoing hip surgery: a systematic review and meta-analysis. Medicina (Kaunas) 2023; 59: 1904.

[10] Hao Y, Li W, Zheng M, Li X, Wu X, Yu Z, Liu S, Li J and Xu H. Effects of liposomal bupivacaine in preoperative fascia iliac block on postoperative pain and delirium in elderly patients undergoing hip fracture surgery: a study protocol for a randomised, parallel controlled prospective clinical study. BMJ Open 2024; 14: e079067.

[11] Peterson ML, Mans C and Doss GA. Subcutaneous hydromorphone hydrochloride provides antinociception with transient adverse effects in four-toed hedgehogs (Atelerix albiventris). J Am Vet Med Assoc 2024; 262: 1-6.

[12] Monopoli MR, Guzman DS, Paul-Murphy J, Beaufrère H and Hawkins MG. Evaluation of thermal antinociceptive effects of intramuscular hydromorphone hydrochloride in great horned owls (Bubo virginianus). J Avian Med Surg 2023; 37: 209-216.

[13] Wang Y, Zhao L, Wu M, An Q, Guo Q, Fan C and Guo Z. Different doses of nalmefene combined

with hydromorphone hydrochloride for postoperative analgesia after colorectal surgery: a randomized controlled study. BMC Surg 2024; 24: 3.
[14] Moran T, Prabhakar A, Diaz JH and Kaye AD. Hydromorphone hydrochloride use during various interventional radiology procedures-pain control and adverse events: a case series audit analysis. Pain Ther 2017; 6: 217-225.
[15] Pan Y, Wang Y, Lie D, Liu D, Chen X, Wu Z, Chen L, Wang H, Peng L, Liang H, Song X and Zhao B. Effectiveness of analgesia with hydromorphone hydrochloride for postoperative pain following surgical repair of structural congenital malformations in children: a randomized controlled trial. BMC Anesthesiol 2021; 21: 192.
[16] Goudman L, Pilitsis JG, Billet B, De Vos R, Hanssens K, Billot M, Roulaud M, Rigoard P and Moens M. The level of agreement between the numerical rating scale and visual analogue scale for assessing pain intensity in adults with chronic pain. Anaesthesia 2024; 79: 128-138.
[17] Chen L, Zhang M, Yu W, Yu J, Cui Q, Chen C, Liu J, Huang L, Liu J, Yu W, Li W, Zhang W, Yan M, Wu J, Wang X, Song J, Zhong F, Liu X, Wang X, Li C, Tan Y, Sun J, Li W and Lü Y. A fully automated mini-mental state examination assessment model using computer algorithms for cognitive screening. J Alzheimers Dis 2024; 97: 1661-1672.
[18] Zhang K, Miao X, Jiang L, Cui S, Liu Z and Wang Z. Postoperative analgesic efficacy and safety of imrecoxib versus celecoxib in hip osteoarthritis patients undergoing total hip arthroplasty: a multi-center, randomized, controlled, noninferiority study. Inflammopharmacology 2023; 31: 1813-1822.
[19] Zhu Y, Li Q, Liu G, Sheng F, Zhang X, Jiang L, Li S, He J, Zou Z, Zhang B, Wang C, Jiang X and Zhao Y. Effects of esketamine on postoperative rebound pain in patients undergoing unilateral total knee arthroplasty: a single-center, randomized, double-blind, placebo-controlled trial protocol. Front Neurol 2023; 14: 1179673.
[20] Song Y, He Q, Huang W, Yang L, Zhou S, Xiao X, Wang Z and Huang W. New insight into the analgesic recipe: a cohort study based on smart patient-controlled analgesia pumps records. Front Pharmacol 2022; 13: 988070.
[21] Badeaux J, Bonanno L and Au H. Effectiveness of ondansetron as an adjunct to lidocaine intravenous regional anesthesia on tourniquet pain and postoperative pain in patients undergoing elective hand surgery: a systematic review protocol. JBI Database System Rev Implement Rep 2015; 13: 27-38.
[22] Orhan Ö, Sezgin EA, Güngör İ, Çetinkaya M, Ataoğlu MB and Kanatlı U. Interscalene block applied by an experienced anesthesiologist has a good anesthetic effect, a long duration of action, and less postoperative pain after arthroscopic shoulder procedures independent of surgery type and operation duration. Jt Dis Relat Surg 2023; 34: 445-450.
[23] Gumusoglu AY, Kabuli HA, Cikot M, Isıksacan N, Kasapoglu P, Cayırcı EC, Binboga S, Karabulut M and Alıs H. The importance of inflammatory markers in detection of complications in patients with gastric cancer undergoing the enhanced recovery after surgery (ERAS) protocol: a prospective cohort study. Wideochir Inne Tech Maloinwazyjne 2022; 17: 688-698.
[24] Nelson AM, Erdmann AA, Coe CL, Juckett MB, Morris K, Knight JM, Hematti P and Costanzo ES. Inflammatory cytokines and depression symptoms following hematopoietic cell transplantation. Brain Behav Immun 2023; 112: 11-17.
[25] Lei M, Wang Y, Chen Q, Huang P, Li Y, Jia Y and Meng D. Changes in serum levels of pain mediators in hemiplegic shoulder pain. Brain Behav 2023; 13: e3289.
[26] Sun Z, Qu X, Wang T, Liu F and Li X. Effects of warm acupuncture combined with meloxicam and comprehensive nursing on pain improvement and joint function in patients with knee osteoarthritis. J Healthc Eng 2022; 2022: 9167956.
[27] Memtsoudis SG, Stundner O, Yoo D, Gonzalez Della Valle A, Boettner F, Bombardieri AM, Jules-Elysee K, Poultsides L, Ma Y and Sculco TP. Does limb preconditioning reduce pain after total knee arthroplasty? A randomized, double-blind study. Clin Orthop Relat Res 2014; 472: 1467-1474.
[28] Xu W, Xiao Y, Zhao M, Zhu J, Wang Y, Wang W, Wang P and Meng H. Effective treatment of knee osteoarthritis using a nano-enabled drug acupuncture technology in mice. Adv Sci (Weinh) 2023; 10: e2302586.
[29] Bruno RR, Wolff G, Wernly B, Masyuk M, Piayda K, Leaver S, Erkens R, Oehler D, Afzal S, Heidari H, Kelm M and Jung C. Virtual and augmented reality in critical care medicine: the patient's, clinician's, and researcher's perspective. Crit Care 2022; 26: 326.
[30] Shen L, Jiang Z, Wang Q and Xu W. Topical use of tranexamic acid can reduce opioid consumption compared with intravenous use for patients undergoing primary total hip arthroplasty: a prospective randomized controlled trial. BMC Musculoskelet Disord 2023; 24: 455.
[31] Yuan M, Ding Z and Zhou Z. A commentary on "Effects of edaravone on postoperative cognitive function in elderly patients undergoing hip joint replacement surgery: a randomized con-

trolled trial" [Int. J. Surg. 80 (2020) 13-18]. Int J Surg 2020; 82: 30-31.
[32] Jurewicz A, Gasiorowska A, Leźnicka K, Pawlak M, Sochacka M, Machoy-Mokrzyńska A, Bohatyrewicz A, Maciejewska-Skrendo A and Pawlus G. Individual factors modifying postoperative pain management in elective total hip and total knee replacement surgery. Life (Basel) 2024; 14: 211.
[33] Li JQ, Yuan H, Wang XQ and Yang M. Dexmedetomidine-induced anesthesia in elderly patients undergoing hip replacement surgery. World J Clin Cases 2023; 11: 3756-3764.
[34] Huai X, Jiao Y, Gu X, Zhu H, Chen L, Fan Y, Yu W, Su D and Xie H. Preoperative chronic pain as a risk factor for early postoperative cognitive dysfunction in elderly patients undergoing hip joint replacement surgery: a prospective observational cohort study. Front Neurosci 2021; 15: 747362.
[35] Oh CS, Lim HY, Jeon HJ, Kim TH, Park HJ, Piao L and Kim SH. Effect of deep neuromuscular blockade on serum cytokines and postoperative delirium in elderly patients undergoing total hip replacement: a prospective single-blind randomised controlled trial. Eur J Anaesthesiol 2021; 38 Suppl 1: S58-S66.
[36] Lin X, Tang J, Liu C, Li X, Cao X, Wang B, Dong R, Xu W, Yu X, Wang M and Bi Y. Cerebrospinal fluid cholinergic biomarkers are associated with postoperative delirium in elderly patients undergoing total hip/knee replacement: a prospective cohort study. BMC Anesthesiol 2020; 20: 246.