ORIGINAL ARTICLE

UDC: 617-089.168-051.9:616.8-009.7-085
DOI: https://doi.org/10.2298/VSP230606003X

Effect of butorphanol tartrate combined with dexmedetomidine on postoperative analgesia

Efekat kombinacije butorfanol tartarata sa deksmedetomidinom na postoperativnu analgeziju

[1]Xiaofeng Xu*, [1]Linsen Zhan*, Huarong Lu†, Gongmin Yu*, Changxing Xia*, Yongqing Xu‡, Gang Liu*, Yuhui Chai*, Yunping Lan*

***The Quzhou Affiliated Hospital of Wenzhou Medical University, Quzhou People's Hospital, Department of Anesthesiology, Quzhou, Zhejiang Province, China; †Jiangshan People's Hospital of Zhejiang Province, Jiangshan, Zhejiang Province, China; ‡People's Hospital of Changshan, Changshan, Zhejiang Province, China**

[1]both authors contributed equally to this study.

Abstract

Background/Aim. Since finding a safe and efficient strategy of multimodal postoperative analgesia and sedation is particularly critical, it is important that dexmedetomidine (DM) combined with opioid anesthetics can enhance that through a synergistic action. The aim of the study was to assess the effect of butorphanol tartrate (BT) combined with DM on postoperative analgesia. **Methods.** A total of 100 elderly patients undergoing general anesthesia surgery from January 2019 to June 2022 were selected. The patients were divided into two equal groups – research group (RG) and control group (CG), using the random number table method. All patients were given postoperative patient-controlled intravenous analgesia (PCIA) plus background infusion. CG patients were given 10 mg of BT, and RG patients were given 10 mg of BT and 300 μg of DM. The analgesics were diluted in 100 mL of 0.9% normal saline. The doses of rescue analgesic tramadol within 48 hrs after surgery, the number of PCIA boluses 48 hrs after surgery, and postoperative hospitalization time were recorded. The Visual Analog Scale (VAS) score, Ramsay sedation score (RSS), inflammatory and stress responses [interleukin (IL)-6, interferon (IFN)-γ, and angiotensin II (Ang-II)], and anesthesia-related adverse reactions (ARAR) were compared at different time points. **Results.** The dose of tramadol within 48 hrs after surgery, the number of PCIA boluses 48 hrs after surgery, and the postoperative hospitalization time of RG were lower than those of CG ($p < 0.05$). VAS scores at rest and during activity and serum IL-6, IFN-γ, and Ang-II levels of both groups increased at 4 and 12 hrs after surgery, then decreased at 24 hrs after surgery. The above indicators of RG were lower than those of CG at each time point ($p < 0.05$). The RSSs of the two groups increased at 4, 12, and 24 hrs after surgery, then dropped at 48 hrs after surgery. The scores of RG were lower than those of CG at each time point ($p < 0.05$). The incidence rates of ARAR had no significant difference between RG and CG ($p > 0.05$). **Conclusion.** BT combined with DM is effective for analgesia and sedation after general anesthesia surgery in elderly patients, which can reduce inflammatory and stress responses without increasing ARAR.

Key words:
analgesia, patient-controlled; anesthesia, general; dexmedetomidine; drug-related side effects and adverse reactions; pain, postoperative.

Apstrakt

Uvod/Cilj. Imajući u vidu da je pronalaženje bezbedne i efikasne multimodalne postoperativne analgezije i sedacije posebno kritično, važno je da deksmedetomidin (DM) u kombinaciji sa opioidnim anesteticima to može poboljšati sinergističkim delovanjem. Cilj rada bio je da se proceni efekat butorfanol tartarata (BT) u kombinaciji sa DM na postoperativnu analgeziju. **Metode.** Odabrano je ukupno 100 starijih bolesnika koji su bili podvrgnuti operaciji u opštoj anesteziji u periodu od januara 2019. do juna 2022. godine. Bolesnici su nasumično podeljeni u dve jednake grupe – istraživačku grupu (IG) i kontrolnu grupu (KG). Svim bolesnicima je data postoperativna intravenska analgezija koju kontroliše bolesnik (*postoperative patient-controlled intravenous analgesia* – PCIA) uz kontinuiranu infuziju. Bolesnicima KG dato je 10 mg BT, a bolesnicima IG, 10 mg BT i 300 μg DM. Analgetici su razblaženi u

Correspondence to: Yunping Lan, The Quzhou Affiliated Hospital of Wenzhou Medical University, Quzhou People's Hospital, Department of Anesthesiology, Quzhou 324000, Zhejiang Province, China. Email: yubiping3067@163.com

100 mL fiziološkog rastvora. Beležene su doze datog tramadola u prvih 48 sati od operacije i broj bolusa postoperativne PCIA 48 sati posle operacije, kao i dužina postoperativne hospitalizacije. Skor Vizuelne analogne skale (VAS), Remzijev skor sedacije (RSS), odgovor na inflamaciju i stres [interleukin (IL)-6, interferon (IFN)-γ i angiotenzin II (Ang-II)] i neželjene reakcije povezane sa anestezijom (NRPA) upoređivane su u različitim vremenskim tačkama. **Rezultati.** Broj doza tramadola u prvih 48 sati nakon operacije, broj bolusa PCIA 48 sati nakon operacije i dužina postoperativne hospitalizacije bili su manji u IG nego u KG ($p < 0,05$). Skorovi VAS u mirovanju i tokom aktivnosti kao i detektovani nivoi IL-6, IFN-γ, i Ang-II u serumu u obe grupe bili su povećani 4 i 12 sati posle operacije, a sniženi 24 sata posle operacije. Navedeni pokazatelji za IG bili su niži od pokazatelja za KG u svakoj tački merenja ($p < 0,05$). RSS u obe grupe povećao se 4, 12 i 24 sata posle operacije, a zatim opao 48 sata posle operacije. Skorovi za IG bili su niži od onih za KG na svakoj tački merenja ($p < 0,05$). Nije bilo statistički značajne razlike u stopi incidencije NRPA između IG i KG ($p > 0,05$). **Zaključak.** Kombinacija BT sa DM efikasna je za analgeziju i sedaciju posle operacije u opštoj anesteziji kod starijih bolesnika, što može smanjiti odgovor na inflamaciju i stress bez povećanja NRPA.

Ključne reči:
analgezija, kontrolisana od strane bolesnika; anestezija, opšta; deksmedetomidin; lekovi, neželjeni efekti i neželjene reakcije; bol, postoperativni.

Introduction

Patient-controlled intravenous analgesia (PCIA) is a common multimodal analgesic strategy following general anesthesia surgery (GAS), in which analgesics are continuously pumped into the patient at a specific speed to reduce the pain degree and keep the stability of vital signs [1, 2]. Opioids are the major analgesic substance. The analgesic effect of butorphanol tartrate (BT), a mixed agonist-antagonist opioid receptor, is 30–40 times greater than that of pethidine or about 7 times greater than that of morphine, which is beneficial for relieving visceral pain. However, postoperative high-dose use will increase gastrointestinal reactions, drowsiness, and other adverse reactions (AR) and exert little sedative effect [3, 4]. Therefore, finding a safe and efficient strategy for multimodal postoperative analgesia (PA) and sedation is particularly critical. Dexmedetomidine (DM) is a novel, highly selective α2-adrenergic receptor agonist that can effectively inhibit norepinephrine and central adrenaline levels and exert anti-sympathetic, anti-anxiety, analgesic, and neuroprotective effects [5]. It has been found that DM combined with opioid anesthetics can enhance postoperative sedation and analgesia through a synergistic action [6, 7]. However, the use of BT combined with DM in PA in elderly patients undergoing GAS is rarely reported in China and foreign countries.

In view of this, 100 patients undergoing GAS were selected in this study to assess the effect of BT combined with DM on PA.

Methods

General data

The sample size was determined according to pre-experiments. In this prospective study, a total of 100 elderly patients undergoing GAS at the Quzhou People's Hospital (Quzhou) from January 2019 to June 2022 were selected and divided into a control group (CG) and a research group (RG) (50 patients in each group) using the random number table method. This study has been approved by the Ethics Committee of Quzhou People's Hospital.

Inclusion and exclusion criteria

Inclusion criteria were as follows: 1) patients requiring PA; 2) patients in grades I and II of the American Society of Anesthesiologists (ASA); 3) patients undergoing general anesthesia; 4) patients with normal audio-visual function and intelligence before surgery; 5) patients not allergic to the drugs used in this study; 6) patients who and whose families voluntarily signed the informed consent form.

Exclusion criteria were as follows: 1) patients who used sedatives, analgesics, or antidepressants for a long time; 2) patients with a history of immunotherapy, chronic pain, or cerebrovascular disease; 3) patients accompanied by atrioventricular block or sinus bradycardia; 4) patients undergoing emergency surgery; 5) patients with uncontrolled preoperative blood pressure (BP) > 180/100 mmHg; 6) patients with infectious diseases, immune, hematopoietic, or coagulation dysfunction.

Anesthesia and analgesia methods

After the patient was sent to the operating room, venous access was established, and electrocardiogram and vital signs were routinely monitored. NICAP-18, a non-invasive continuous BP monitoring system (Zhejiang Mailian Medical Devices Co., Ltd., China), was used. The wrist splint was fixed before anesthesia induction. Subsequently, the DSA-T-C disposable non-invasive pressure sensor (Zhejiang Mailian Medical Devices Co., Ltd., China) and NICAP-18 system were put on the same level. Then, the probe automatically searched for the strongest position of the artery to perform real-time BP monitoring.

Anesthesia induction: After tracheal intubation, the anesthesia machine was connected to deliver 1.5 mg/kg propofol, 0.04 mg/kg midazolam, 0.3 μg/kg sufentanil, and 0.2 mg/kg cisatracurium besilate, and the respiration was controlled. Anesthesia maintenance: propofol (4–8 mg/kg/hr) and remifentanil (0.1–0.3 μg/kg/min) were continuously pumped, and cisatracurium besilate was intravenously injected intermittently. After the surgery, the patient was sent to the recovery room, the tracheal tube was withdrawn, and the PCIA pump was connected for PA.

PA: For CG, 10 mg of BT (Shanghai Hengrui Pharmaceutical Co., Ltd., 10 mg/mL, 1 mg of BT *per* spray) was pumped. For RG, 10 mg of BT and 300 μg of DM [Jiangsu Hengrui Pharmaceuticals Co., Ltd., China; 200 μg : 2 mL (calculated based on DM)] was pumped. The analgesics were diluted in 100 mL of 0.9% normal saline. PCIA plus background infusion were performed: PCIA dose of 1 mL/each time, background infusion rate of 2 mL/h, and lockout time of 15 min. When the Visual Analogue Scale (VAS) score was ≥ 4 points, 100 mg tramadol was injected intramuscularly for rescue analgesia. The patient returned to the ward when the Modified Aldrete Score was > 9 points.

Observation indicators

Analgesic and sedative effects: At 4, 12, 24, and 48 hrs after the surgery [8, 9], the pain degree of patients in an active state (turning over) and a resting state (lying quietly) was assessed using the VAS score. The VAS score ranges from 0 to 10 points – a lower score indicates milder pain. Meanwhile, sedation was assessed by the Ramsay sedation score (RSS) [10]: 1 point (dysphoria); 2 points (awake, quiet, and cooperative); 3 points (drowsiness but quick response to physical stimulation and instruction); 4 points (light sleep and able to be quickly awakened); 5 points (asleep and slow response to stimulation and instruction); 6 points (deep sleep and no response to any stimulation and instruction).

The dose of rescue analgesic tramadol within 48 hrs after surgery, the number of PCIA boluses 48 hrs after surgery, and postoperative hospitalization time were recorded.

Inflammatory and stress responses: 3 mL of venous blood was collected from each patient in each group before surgery (15 min before anesthesia) and at 12, 24, and 48 hrs after surgery, and centrifuged (radius: 6 cm, speed: 2,500 revolutions/min) for 10 min. Then the supernatant was harvested to measure the levels of interleukin (IL)-6, interferon IFN)-γ, and angiotensin II (Ang-II) by enzyme-linked immunosorbent assay using kits purchased from Shanghai LabEx Biotech Co., Ltd., China.

Anesthesia-related AR, including nausea and vomiting, dizziness, rash, delirium, and respiratory depression, were observed three days after the surgery.

Statistical analysis

SPSS 24.0 software (IBM Inc., USA) was used for statistical analysis. All the measurement data were subjected to the normal distribution test, and the normally distributed ones were described by mean ± standard deviation. The repeated measures data were analyzed using analysis of variance (F), and the least significant difference *t*-test was used for further pairwise comparison. The non-normally distributed measurement data were described by median (M) interquartile boundary values (P_{25}, P_{75}), and the Kruskal-Wallis rank sum test was used for comparison between groups. When there were significant intergroup differences, the Dunn's test was further employed for multiple comparisons. The count data were expressed in percentages, and the χ^2 test was performed; $p < 0.05$ was considered statistically significant.

Results

General data

There were 55 males and 45 females aged 60–81 years, with an average of 69.32 ± 3.84 years. The body mass index (BMI) was 19.34–25 kg/m^2, with an average of 22.54 ± 1.86 kg/m^2. There were 53 cases of ASA grade I and 47 cases of grade II. The surgery was conducted on the abdomen in 22 cases, the chest in 20 cases, the pelvis in 18 cases, the bone in 35 cases, and other sites in 5 cases. No significant differences were found concerning gender, age, BMI, ASA grade, and surgical site between RG and CG ($p > 0.05$) (Table 1).

Use of tramadol, number of PCIA boluses, and postoperative hospitalization time

The dose of tramadol within 48 hrs after surgery, the number of PCIA boluses 48 hrs after surgery, and the postoperative hospitalization time of RG were lower than those of CG ($p < 0.05$) (Table 2).

Analgesic and sedative effects

Both groups' resting and active VAS scores increased at 4 and 12 hrs after surgery, then decreased at 24 hrs after surgery. The above indicators of RG were lower than those

Table 1

General data of the two groups

Group	Male/Female	Age (years)	BMI (kg/m^2)	ASA grade	Surgical site
				I/II	abdomen/chest/pelvis/bone/other
Control	26/24	69.82 ± 3.45	22.86 ± 1.72	27/23	12/9/10/17/2
Research	29/21	68.82 ± 4.76	22.34 ± 1.81	26/24	10/11/8/18/3
t/χ^2	0.364	1.203	1.473	0.040	0.833
p	0.546[a]	0.232[b]	0.144[b]	0.841[a]	0.934[a]

ASA – American Society of Anesthesiologists; BMI – body mass index.
For each group the number of patients enrolled was 50.
[a] – the χ^2 test was used for the comparison of count data; [b] – the *t*-test was used for the comparison of measurement data.
All values are expressed as mean ± standard deviation or number.

of CG at each time point ($p < 0.05$). RSS of the two groups increased at 4, 12, and 24 hrs after surgery, then dropped at 48 hrs after surgery. The scores of RG were lower than those of CG at each time point ($p < 0.05$) (Table 3).

Inflammatory and stress responses

Serum IL-6, IFN-γ, and Ang-II levels of both groups increased at 4 and 12 hrs after the surgery, then decreased at 24 hrs after surgery. The above indicators of RG were lower than those of CG at each time point ($p < 0.05$) (Table 4).

Anesthesia-related adverse reactions

The incidence rates of anesthesia-related AR had no significant difference between RG (22%) and CG (28%) ($p > 0.05$) (Table 5).

Table 2

Use of tramadol, number of PCIA boluses, and postoperative hospitalization time

Group	Dose of tramadol (mg/day)	Number of PCIA boluses 48 hrs after surgery	Postoperative hospitalization time (days)
Control	62.35 ± 7.45	24.84 ± 4.02	7.85 ± 2.35
Research	54.07 ± 6.35	21.04 ± 3.54	6.02 ± 1.25
t	5.981	5.016	4.862
p	< 0.001[a]	< 0.001[a]	< 0.001[a]

PCIA – patient-controlled intravenous analgesia; For each group the number of patients enrolled was 50.
[a] – the *t*-test was used for the comparison of measurement data.
All values are expressed as mean ± standard deviation.

Table 3

Visual analog scale and Ramsay sedation scores at different time points after the surgery

Group/time point after the surgery	Visual analog scale score		Ramsay sedation score
	resting	active	
Control			
4 hrs	2.86 ± 0.28	3.32 ± 0.48	3.52 (1.25, 6.86)
12 hrs	3.37 ± 0.43	4.02 ± 0.52	3.85 (1.31, 7.35)
24 hrs	3.12 ± 0.38	3.72 ± 0.43	3.97 (1.28, 7.85)
48 hrs	2.43 ± 0.22	3.13 ± 0.28	3.42 (1.28, 7.54)
Research			
4 hrs	2.18 ± 0.32	2.76 ± 0.51	3.15 (1.18, 5.85)
12 hrs	2.86 ± 0.41	3.34 ± 0.61	3.32 (1.25, 5.89)
24 hrs	2.64 ± 0.3	3.15 ± 0.28	3.54 (1.27, 6.05)
48 hrs	2.03 ± 0.19	2.46 ± 0.33	3.51 (1.33, 6.15)
$F_{intergroup}/p_{intergroup}$ or $U_{integroup}/p_{intergroup}$	51.623/< 0.001	41.725/< 0.001	77.586/< 0.001
$F_{time\ point}/p_{time\ point}$ or $U_{time\ point}/p_{time\ point}$	81.623/< 0.001	71.824/< 0.001	153.652/< 0.001
$F_{crossover}/p_{crossover}$ or $U_{crossover}/p_{crossover}$	251.362/< 0.001	218.513/< 0.001	325.521/< 0.001

For each group the number of patients enrolled was 50.
All values are expressed as mean ± standard deviation or median [interquartile boundary values (P_{25}–P_{75})].

Table 4

Inflammatory and stress responses before and after the surgery (ng/L)

Group/time point after the surgery	IL-6	IFN-γ	Ang-II
Control			
4 hrs	21.03 ± 4.51	312.52 ± 20.16	245.26 ± 24.51
12 hrs	61.24 ± 6.35	400.12 ± 26.35	312.25 ± 32.42
24 hrs	50.18 ± 5.52	386.08 ± 31.42	281.65 ± 30.36
48 hrs	39.64 ± 4.18	348.26 ± 28.42	264.85 ± 27.65
Research			
4 hrs	20.98 ± 5.02	310.89 ± 21.42	243.32 ± 26.11
12 hrs	48.63 ± 7.81	375.62 ± 25.84	286.65 ± 30.15
24 hrs	37.26 ± 6.61	351.02 ± 21.43	266.36 ± 28.65
48 hrs	29.43 ± 5.82	322.46 ± 19.72	251.85 ± 25.16
$F_{intergroup}/p_{intergroup}$	41.526/< 0.001	38.564/< 0.001	100.251/< 0.001
$F_{time\ point}/p_{time\ point}$	96.625/< 0.001	82.512/< 0.001	154.623/< 0.001
$F_{crossover}/p_{crossover}$	99.658/< 0.001	481.623/< 0.001	602.02/< 0.001

IL-6 – interleukin 6; IFN-γ – interferon gamma; Ang-II – angiotensin II.
For each group the number of patients enrolled was 50.
All values are expressed as mean ± standard deviation or median [interquartile boundary values (P25–P75)].

Table 5

Anesthesia-related adverse reactions

Group	Nausea and vomiting	Dizziness	Rash	Delirium	Respiratory depression	Total
Control	4 (8)	7 (14)	3 (6)	0 (0)	0 (0)	14 (28)
Research	3 (6)	7 (14)	1 (2)	0 (0)	0 (0)	11 (22)
χ^2						0.480
p						0.488

For each group the number of patients enrolled was 50.
All values are expressed as numbers (percentages).

Discussion

The aim of this study was to evaluate the effect of BT in combination with DM on the PA of elderly patients undergoing GAS. We found that this method relieved inflammatory and stress responses without increasing anesthesia-related AR.

Due to the decline of various functions and low tolerance to surgery and anesthesia, elderly patients are more prone to postoperative hyperalgesia, while intense pain can cause central nervous system (CNS) excitation, improve stress responses, and even induce adverse cardiovascular events such as myocardial ischemia in severe cases [11, 12]. BT is a mixed agonist-antagonist opioid receptor with a potent analgesic effect. However, single high-dose administration may lead to deep and excessive sedation and analgesia in elderly patients and worsen the stress response, making it hard to wake the elderly patients up at any time [13, 14]. Ahsan et al. [15] found that DM plus butorphanol could exert a synergistic analgesic effect, benefitting the clinical treatment of acute nociceptive pain, which was regulated by κ-opioid receptors (KORs) and μ-opioid receptors (MORs).

In this study, the dose of tramadol within 48 hrs after surgery, the number of PCIA boluses 48 hrs after surgery, and the postoperative hospitalization time of RG were lower than those of CG. The resting and active VAS scores of both groups peaked at 12 hrs after surgery and then decreased at 24 hrs after surgery. The above indicators of RG were lower than those of CG at each time point. RSSs of the two groups increased at 4, 12, and 24 hrs after surgery, then dropped at 48 hrs after surgery. The scores of RG were lower than those of CG at each time point. Therefore, DM combined with BT can improve the analgesic effect after GAS in elderly patients and prevent agitation. Du et al. [16] found that 300 μg of DM together with 10 mg of butorphanol given by the PCIA pump after radical mastectomy could help relieve pain and reduce the times of pump pressing. Shi and Gan [17] reported that compared with 0.1 mg/kg butorphanol alone, in combination with 0.1 μg/kg/hr of DM could raise RS, lower the VAS score, and reduce the incidence of nausea, vomiting, dizziness, and other AR, which is consistent with the findings in this study. The above results verify again that DM combined with butorphanol has good postoperative analgesic and sedative effects, and its possible mechanisms are as follows: DM regulates nociceptive signaling in CNS by stimulating spinal cord α2-receptors; DM can activate presynaptic membrane α2-receptors, reduce the activation and tension of sympathetic nerves, inhibit the secretion and release of norepinephrine, and reduce the central sympathetic outflow, thereby terminating the diffusion of pain signals [18, 19]. In addition, butorphanol can antagonize or excite μ-receptors with a long duration of analgesia. It has almost no activity on δ-receptors, thus reducing anxiety and irritability [20]. As a potent and selective agonist of κ receptors, butorphanol is beneficial in relieving pain. BT can stimulate opioid receptors such as KORs and MORs, induce the hyperpolarization of the inner opioid neuron cell membrane, reduce the levels of pain-causing substances, and inhibit the release of noxious neurotransmitters such as substance P [21, 22]. Despite different mechanisms, BT combined with DM can, through a complementary and synergistic effect, enhance the sedative and analgesic effects, improve the pain threshold of patients, and reduce the sensitivity to pain and trauma.

Hyperalgesia is an important mechanism of pain, and its molecular basis lies in the synergism of neurogenic inflammatory response and the generation of pain-causing factors [23]. When stimulated by trauma, surgery, and anesthesia, the body will release a large number of pain-causing factors and nerve growth factors, thereby increasing further the permeability of the cell membrane and enhancing central sensitization, peripheral sensitization, and inflammatory cascade. As a result, pain signal transmission is facilitated. In this study, serum IL-6, IFN-γ, and Ang-II levels of both groups increased at 4 and 12 hrs after surgery, then decreased at 24 hrs after surgery. The above indicators of RG were lower than those of CG at each time point. Thus, elderly patients had inflammatory and stress responses following GAS. Nevertheless, BT combined with DM can reduce the inflammatory and stress responses, which may also be one of the analgesic mechanisms of the drug combination. In terms of safety, the incidence rate of anesthesia-related AR in RG was lower than that in CG in this study. The reason is that the incidence of adverse drug reactions is increased due to a low diffusion rate of a single drug through blood, while BT combined with DM is characterized by high metabolism speed and short onset time and can also reduce the dosage of BT and prevent overdose-induced AR. Moreover, DM can weaken gastrointestinal peristalsis through synaptic regulation, inhibit gastric secretion, and resist vomiting and nausea, thereby reducing gastrointestinal AR. However, the incidence of AR was not significantly different between the two groups.

Nevertheless, this study is limited. The sample size is small, and the follow-up time is short; hence, it is necessary to increase the sample size further and prolong the follow-up time to confirm our findings.

Conclusion

In conclusion, BT combined with DM is effective in analgesia and sedation after GAS in elderly patients, which can regulate levels of serum pain mediators and reduce inflammatory and stress responses without increasing anesthesia-related AR. This study provides novel insights into clinical treatment in the future.

Acknowledgement

This study was financially supported by the Clinical Research Fund Project of Zhejiang Medical Association (No. 2015ZYC-A100 and 2017ZYC-A111).

Conflict of interest

The authors declare no conflict of interest.

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Received on July 6, 2023
Revised on August 24, 2023
Revised on December 6, 2023
Accepted on December 19, 2023
Online First January 2024