

The Optimal Administration Time of Butorphanol in Suppressing Sufentanil-induced Cough: A Single-Center Randomized Double-Blind Trial

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Abstract

Background: To evaluate the optimal administration time of butorphanol in suppressing sufentanil-induced cough(SIC) during the induction of general anesthesia.

Methods:180 patients were randomly divided into 4 equally sized groups: at 5min, 2min and 0min before anesthesia induction, all patients were sequentially injected the drug labeled A/B/C (butorphanol 1mg or normal saline), GI received intravenously drug A/B/C (All were normal saline),GII received intravenously drug A/B/C (A was butorphanol, B and C were saline), GIII received intravenously drug A/B/C (B is butorphanol, A and C were saline), GIV received intravenously drug A/B/C (C is butorphanol, A and B were saline). ALL Patients were then administrated with sufentanil 0.4 µg/kg in 5s after drug C. The incidence and severity of SIC was recorded within 2 minutes after sufentanil injection. MAP, HR, and SpO₂ were recorded at T0 (before the administration of any drug),Ta, Tb, Tc (before the injection of drug A/B/C), T1(2minutes after sufentanil injection) and T2 (1 minutes after endotracheal intubation).

Results: The incidences of cough in GII, GIII, and IV were lower than that in GI (0.09, 0.01, and 0 vs 42.2%, $P<0.01$), while there were no significant differences between GII, GIII, and GIV. The HR of all 4 groups at T2 were significantly higher than their levels at any other time ($P<0.05$,T2 vs other time), but there's no significant difference among 4 groups at T2. The MBP of all 4 groups at Ta and Tb were significantly lower than their levels at any other time ($P<0.05$, Ta and Tb vs other time), but there's no significant difference among 4 groups at Ta and Tb. At Ta, the SpO₂ of GII was significantly lower than GI, GIII and GIV ($P<0.05$); at Tb, the SpO₂ of GII was significantly lower than GI ($P<0.05$) and GIV ($P<0.01$); at Tc, the SpO₂ of GIII were significantly lower than GIV ($P<0.05$).

Conclusion: Intravenous butorphanol 1 mg could effectively suppress SIC before sufentanil injection. Without waiting time before administering the sufentanil may be feasible in clinical practice, it has the same suppressive effect and has no influence on BP, HR, SpO₂ and the total amount of sufentanil.

Trial registration: Chinese Clinical Trial Registry with registration number ChiCTR1900024394. Registered 9 July 2019.

Background

During the induction of anesthesia, sufentanil induced-cough(SIC) is

less likely to attract the attention of clinical anesthesiologists than fentanyl, yet this phenomenon may be undesirable in any patients, the cough rate caused by sufentanil can be as high as 47%^[1].

Several pharmacological measures have been studied to suppress opioid-induced cough, one of these measures was prototypical agonist-antagonist opioid analgesic agents, such as butorphanol^[2], dezocine^[3, 4] and pentazocine^[5], have shown their efficacy in suppressing opioid-induced cough. Butorphanol is considered to be a mixed agonist-antagonist opioid analgesic that has affinity for μ -, δ -,

and κ -opioid receptor subtype (affinity in vitro of 1:4:25), with extensively used in clinical practice due to a potent analgesic effect and minimum side effects^[6, 7]. But the time of administration on preventing SIC is unintelligible, which was ranged from 5 s-15 minutes. When it should be given before sufentanil was still unclear^[8-10], and there is no investigation regarding the administration time of butorphanol on preventing unwanted SIC. So this trial was conducted to evaluate the optimal administration time of butorphanol on preventing SIC during the induction of general anesthesia.

Methods

This trial was approved by the Ethics Committee of Zhongshan Hospital, Fudan University (B2019-129), Shanghai China and registered at www.chictr.org.cn (ChiCTR1900024394). Written informed consent was obtained from all patients. 180 American Society of Anesthesiologists (ASA) physical status I-II patients of both genders, aged 18-65 years, BMI (body mass index) ≤ 30 kg/m² and scheduled for elective surgery under general anesthesia at Zhongshan Hospital from July to December 2019 were screened in this trial. Exclusion criteria included impaired kidney or liver function; Aneurysm; a history of chronic cough, asthma or smoking; upper respiratory tract infection, treatment with angiotensin converting enzyme inhibitors, bronchodilators, or steroids within the previous 2 weeks; pregnancy, lactation and delivery surgery. Patients with increased intracranial, intraocular, or intra-abdominal pressures were also excluded.

Patients were unpremedicated and fasted. After arriving the operation room, a venous pathway was established with an intravenous (IV) cannula (18G) on the dorsum of the forearm, or a 18F catheter on the right internal jugular vein, Ringer lactate was infused at a rate of 4-6 ml/min. Then each patient was received routine electrocardiogram (ECG), pulse oxygen saturation (SpO₂), blood pressure (BP), heart rate (HR). Before anesthetic induction, the pretreatment drug, according to the random numbers, butorphanol (batch 16062232, Hengrui Medicine, Jiangsu, China) or saline was prepared in labeled A, B and C 5 mL syringes outside the operating room by an anesthesiologist who was not involved in the induction of anesthesia.

180 patients were assigned at a 1:1:1:1 ratio to one of 4 groups by using computer-generated table of random numbers: 5 min, 2 min and 0 min before induction, all patients were sequentially injected the drug labeled A, B and C (butorphanol 1 mg or normal saline), group I received intravenously drug A, B and C (All were normal saline, served as a negative control for sufentanil), group II received intravenously drug A, B and C (A was butorphanol, B and C were saline), group III received intravenously drug A, B and C (B is butorphanol, A and C were saline), group IV received intravenously drug A, B and C (C is butorphanol, A and B were saline). ALL Patients were then administrated with sufentanil 0.4 μ g/kg in 5 s after drug C. The incidence and severity of cough was recorded for 2 minutes after sufentanil injection, the severity of cough was graded, based on the numbers of cough, as none (0), mild (1-2), moderate (3-4), and severe (5 or more). If SpO₂ dropped below 95%, manually assisted mask ventilation with oxygen was

applied immediately. Then propofol 2 mg/kg and rocuronium 0.6 mg/kg were given to facilitate tracheal intubation.

During experimental period, the mean arterial pressure(MAP), HR, and SpO₂ were recorded at T0 (before the administration of drugs), Ta, Tb and Tc (just before drug A, B and C injection, T1 (2minutes after sufentanil injection and T2 (1 minute after endotracheal intubation). Intravenous route, surgery type, duration and BMI were also recorded, and after operation, the total amount of sufentanil, postoperative VAS pain score were recorded.

In a pilot study, the incidence of cough induced by 0.4 µg/kg of sufentanil was 40% (20/50) when it was administered within 5 seconds. Therefore, we assumed that if the incidence of cough was reduced by 50%, the effect of butorphanol could be considered statistically significant. To achieve 80% statistical power with $\alpha = 0.05$, We factored in a 10% dropout rate and enrolled 45 patients in each group.

Statistical Analysis: Data are expressed as the mean \pm standard deviation, number, proportion, or percentage. Comparison of age, BMI, surgery duration, the total amount of sufentanil, the VAS pain score and the additional amount of sufentanil were analyzed by one-way Analysis of Variance. The Intravenous route, gender, ASA physical status, incidence of cough, and cough severity were compared using Pearson chi-square test or Fisher's exact test. Comparison of MAP, HR and SpO₂ were analyzed by repeated measures two-way analysis of variance. SPSS20.0 (SPSS Inc, Chicago, IL) and GraphPad Prism5.0 software (GraphPad Software Inc, San Diego, CA) were used for statistical analysis. A P-value of < 0.05 was considered to be significant.

Results

Demographic data

In the present study, 200 patients were recruited and 20 patients were excluded, as they met the exclusion criteria (3 subjects declined participation, 7 had a habit of smoking, 3 had a history of asthma, 2 had impaired liver function and 5 had Aneurysm). Therefore, a total of 180 patients were randomized into 4 groups of 45 each and included in the final analyses. There were no significant differences in age, gender, BMI, ASA status, intravenous route, surgery type, duration the total amount of sufentanil (and) postoperative VAS among the four groups(see Table 1 and Table 2).

Table 1
Patient Characteristics

	Group I(n = 45)	Group II(n = 45)	Group III(n = 45)	Group IV(n = 45)	<i>P</i>
Age	46.8 ± 11.7	48.0 ± 11.7	45.9 ± 11.9	46.6 ± 12.9	0.87
Gender(M/F)	23/22	17/28	21/24	14/31	0.22
BMI	23.9 ± 3.0	23.4 ± 2.4	22.6 ± 2.7	23.7 ± 3.0	0.16
ASA(I/II)	31/14	34/11	35/10	32/13	0.77
Intravenous route	37/8	38/7	36/9	38/7	0.93
Operation time	1.5 ± 0.8	1.6 ± 0.8	1.8 ± 1.0	1.6 ± 1.1	0.62
Total sufentanil	40.4 ± 14.4	38.6 ± 16.7	39.7 ± 14.1	35.8 ± 11.4	0.44
Types of surgery					
General surgery(n)	21	17	21	23	
Gynecological surgery(n)	3	5	2	3	
Urological surgery(n)	5	4	4	2	
Otolaryngology surgery(n)	1	4	2	3	
Thoracic surgery(n)	8	5	5	6	
Neurosurgery(n)	4	3	5	2	
Orthopedic surgery(n)	3	7	6	6	

Table 2
Postoperative VAS

		Group I(n = 45)	Group II(n = 45)	Group III(n = 45)	Group IV(n = 45)
VAS	0	30	31	28	37
	Mild(1-3)	13	13	14	7
	Moderate(4-6)	2	1	1	1
	Severe(7-10)	0	0	0	0
<i>P</i> =		0.28			

Incidence And Severity Of Sic

The incidences of cough in group II, group III, and group IV were lower than that in group I (0.09, 0.01, and 0 vs 42.2%, $P < 0.001$), while there were no significant differences between group II, group III, and group IV. The moderate and severe FIC was not observed in group II, III and IV, but was recorded from 13 patients in group I. (see Table 3)

Table 3
Incidence and severity of sufentanil induced-cough

		Group I(n = 45)	Group II(n = 45)	Group III(n = 45)	Group IV(n = 45)
Severity of cough(n)	none	26	41	44	45
	Mild(1-2)	8	4	1	0
	Moderate(3-4)	3	0	0	0
	Severe(≥ 5)	8	0	0	0
Incidence of cough(n,%)		19(42.22%)	4(0.08%)**	1(0.02%)**	0(0%)**
** $P = 0.001$, compared to Group I					

Hemodynamic Data

The HR of all 4 groups at T2 were significantly higher than their levels at any other time ($P < 0.05$, T2 vs other time in all 4 groups), but there's no significant difference among 4 groups at T2 (Fig. 2). The MBP of all 4 groups at Ta and Tb were significantly lower than their levels at any other time ($P < 0.05$, Ta and Tb vs other time in all 4 groups), but there's no significant difference among 4 groups (Fig. 3). The SpO₂ of group II at Ta were significantly lower than group I, group III and group IV ($P < 0.001$), group II at Tb were significantly lower than group I ($P < 0.05$), and group IV ($P < 0.01$), group III at Tc were significantly lower than group IV ($P < 0.01$) (Fig. 4).

Discussion

In our study, we found that the incidences of cough in group II, group III, and group IV were lower than that in group I (0.09, 0.01, and 0 vs 42.2%, $P < 0.001$), while there were no significant differences between group II, group III and group IV, it means that preemptive infusion of 1 mg butorphanol before sufentanil bolus administration reduced the incidence of SIC. However, SpO₂ of group II at Ta and Tb were significantly lower than other groups, group III at Tc were significantly lower than group IV, the drop of SpO₂ may be due to the butorphanol of respiratory depression, so we can suppose that without waiting time is an effective and clinically feasible method for suppressing sufentanil-induced cough during general anesthesia induction. As for MBP of all 4 groups at Ta and Tb were significantly lower than their

levels at any other time, may be due to the psychological comfort caused by the injection of drugs to the patient.

Sufentanil is an opioid with less impact on hemodynamics and strong analgesic effect, which makes it as an ideal option in anesthesia induction^[11]. However, opioid-induced cough(OIC) caused by injecting sufentanil was commonly observed during the induction of anesthesia. A meta-analysis reported that relational factors of OIC can be divided into 2 aspects: the patients' individual physical conditions (age, sex, smoking and disease history), and the usage of opioids (drug category, dosage, concentration, administration order, injection rate, and site)^[12]. Lin et al^[13].found that only light smoking(< 10 cigarettes per day or < 10 smoking years or < 10 packyears), not heavy smoking, could decrease the frequency of fentanyl-induced cough, but the association between age and incidence of cough was not observed in their study. Oshima et al^[14] .completed a cohort study from 1311 adult patients, these authors reported that increasing age, cigarette smoking were associated with a decreased risk of fentanyl-induced cough. OIC is a risk factor for postoperative nausea and vomiting, which means young female nonsmoker may decrease the incidence of postoperative nausea and vomiting by reducing the happening of OIC^[15]. However, in a randomized, double-blind study, they found no association of age or smoking status on the incidence of cough in any of the groups^[15]. So the relationship between patients' individual physical conditions and OIC is remain controversial. However ,there is no doubt that with the increase of opioids dose and concentration can rise the happening of OIC^[17-19]. While does selection of central or peripheral administration of sufentanil affect opioid induced cough? A prospective, randomized, controlled trial was inconsistent to previous literature,they suggested that sufentanil administered through central vein reduces the occurrence and severity of SIC^[17-19].

The mechanisms of OIC remains unclear, but some theories have been proposed to explain this phenomenon. First, the dualism of opioid receptor, substances like histamine and neuropeptides, released by an action on prejunctional μ -opioid receptors after fentanyl administration^[17-19], Kamei et al^[23].showed that fentanyl enhances the excitability of rapidly adapting receptors to cause cough via the enhancement of histamine release in rat's airways. In our study,intravenous butorphanol without waiting time before general anesthesia induction effectively suppressing sufentanil-induced cough may through this mechanisms.Second, inhibition of central sympathetic outflow causes vagal predominance inducing cough and reflex bronchoconstriction^[24]. Third, pulmonary chemoreflex resulting from the stimulation of C-fiber receptors(Juxta-capillary receptors) or irritant receptors(rapidly adapting receptors) from deformation of the trachea-bronchial wall by tracheal smooth muscle constriction^[25-27]. Finally, Sufentanil and fentanyl preparations are available as citrate salts; there is a possibility that, when sufentanil and fentanyl are injected intravenously, their citrate component may stimulate the pulmonary chemoreflex^[28].

Butorphanol, an agonist-antagonist opioid, can antagonize the μ -receptor or preempted the lung related receptors, to prevent the cough reflex while acting on the C-fiber receptor to inhibit the afferent pathway of the cough reflex^[29-31]. The more possible reason that butorphanol suppressing cough just before

injection of sufentanil could be explained by priming use of butorphanol may result in depletion of neurotransmitters in peripheral nerve fibers^[2], as Hoffmann et al. indicated that the interval between the start of injection and the beginning of signal amplification in the ICA was noted as 'arm-to-head time' (AHT), and AHT was 9.0–22.0 s (14.3 ± 3.0 s; mean ± SD)^[32]. Otherwise, it is hard to explain that butorphanol suppresses cough just before or in the same time to inject sufentanil. Moreover, the administration of intravenous butorphanol prior to induction of anaesthesia helps on better attenuation of the haemodynamic response to laryngoscopy and endotracheal intubation^[33].

There are some limitations that are relevant to our study. First, our butorphanol did not calculate the required dose based on the patient's weight. It has been reported that 0.1 mg butorphanol can also completely inhibit SIC, just 5 seconds right before sufentanil bolus. Second, we did not record the effects of butorphanol on postoperative nausea and vomiting. Third, our study provides evidence for the efficacy of butorphanol in suppressing cough just before the sufentanil injection in clinical practice; but we did not verify the exact mechanisms, more studies need to be performed to reveal the exact mechanism.

Conclusion

We suggest that intravenous butorphanol 1 mg just before the sufentanil bolus, without waiting time is an effective and clinically feasible method for suppressing sufentanil-induced cough during general anesthesia induction.

Declarations

Ethics approval and consent to participate

Ethical approval was given by the institutional ethics committee (Zhongshan Hospital, Fudan University (B2019-129), Shanghai China) and registered at Chinese Clinical Trial Registry with registration number ChiCTR1900024394. Written informed consent of participation is obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XZ analysis, paper writing and most part of clinical studies. SY data mining and part of clinical studies. LQ & CY experimental design, ideal conception, and paper writing. All authors read and approved the final version of the manuscript.

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Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author and author on reasonable request.

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Figures

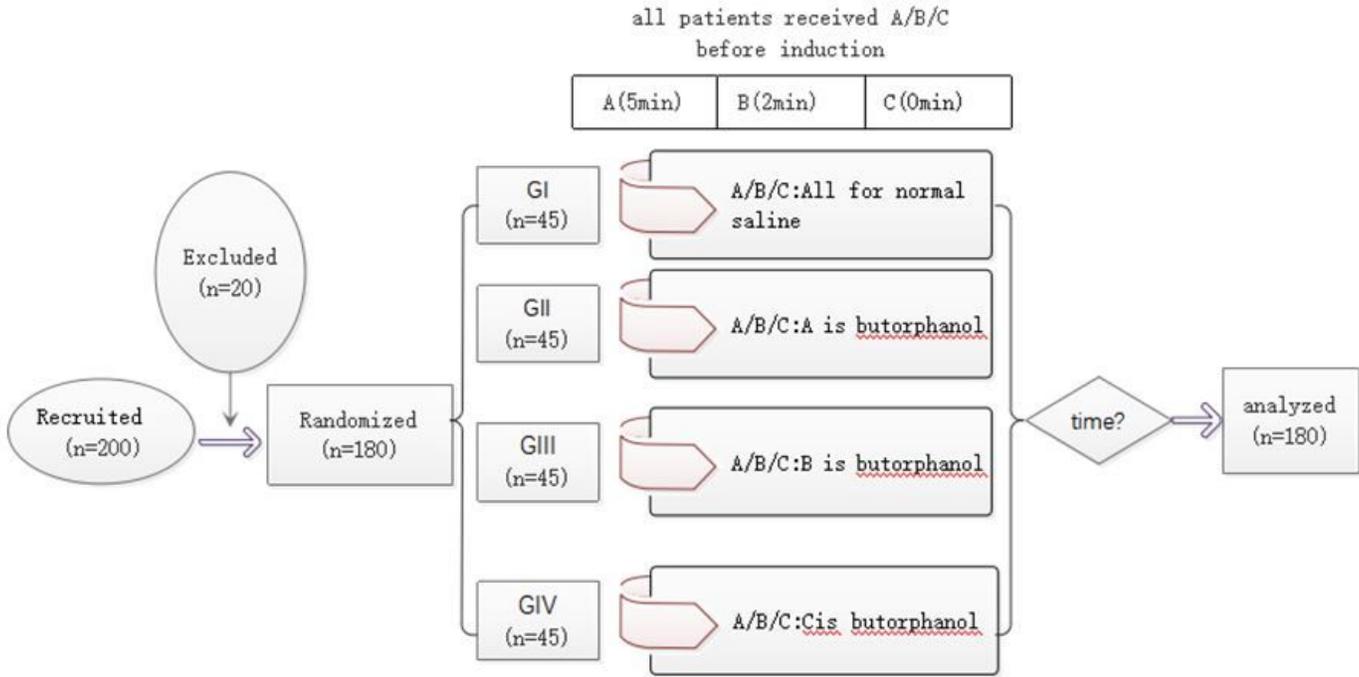


Figure 1

Methods

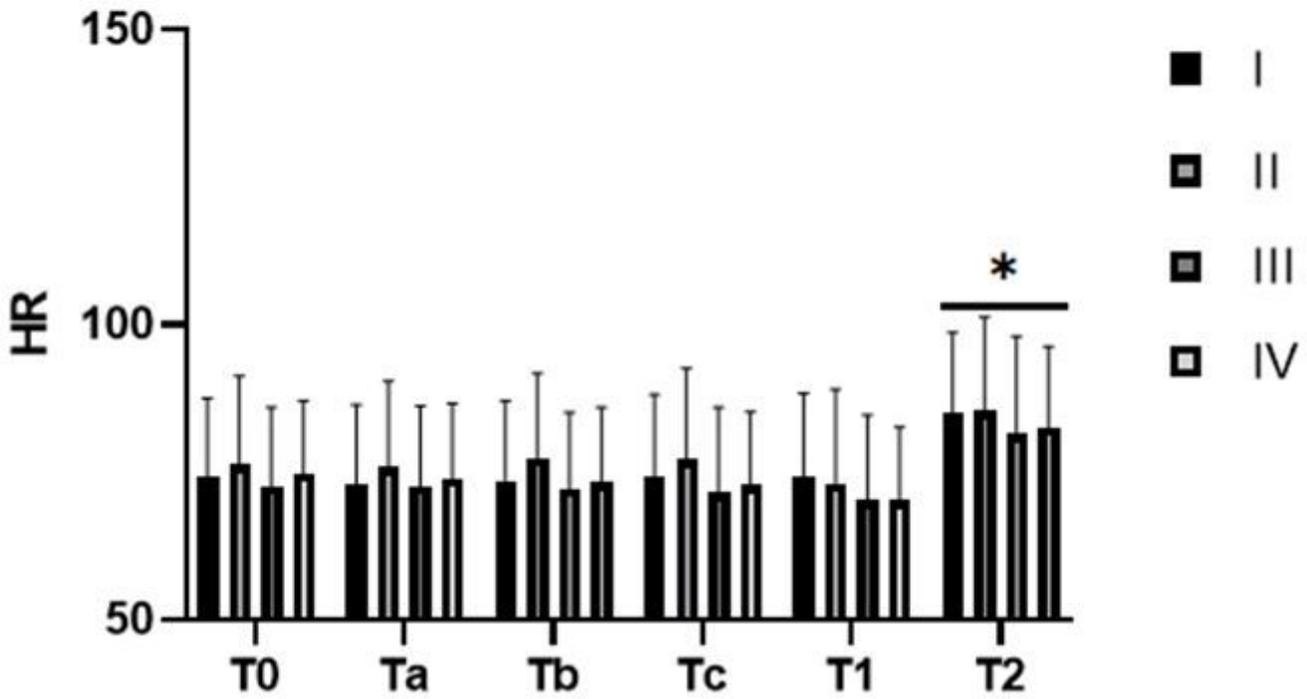


Figure 2

HR at different timepoints. $\square P < 0.05$, T2 vs other time in all 4 groups.

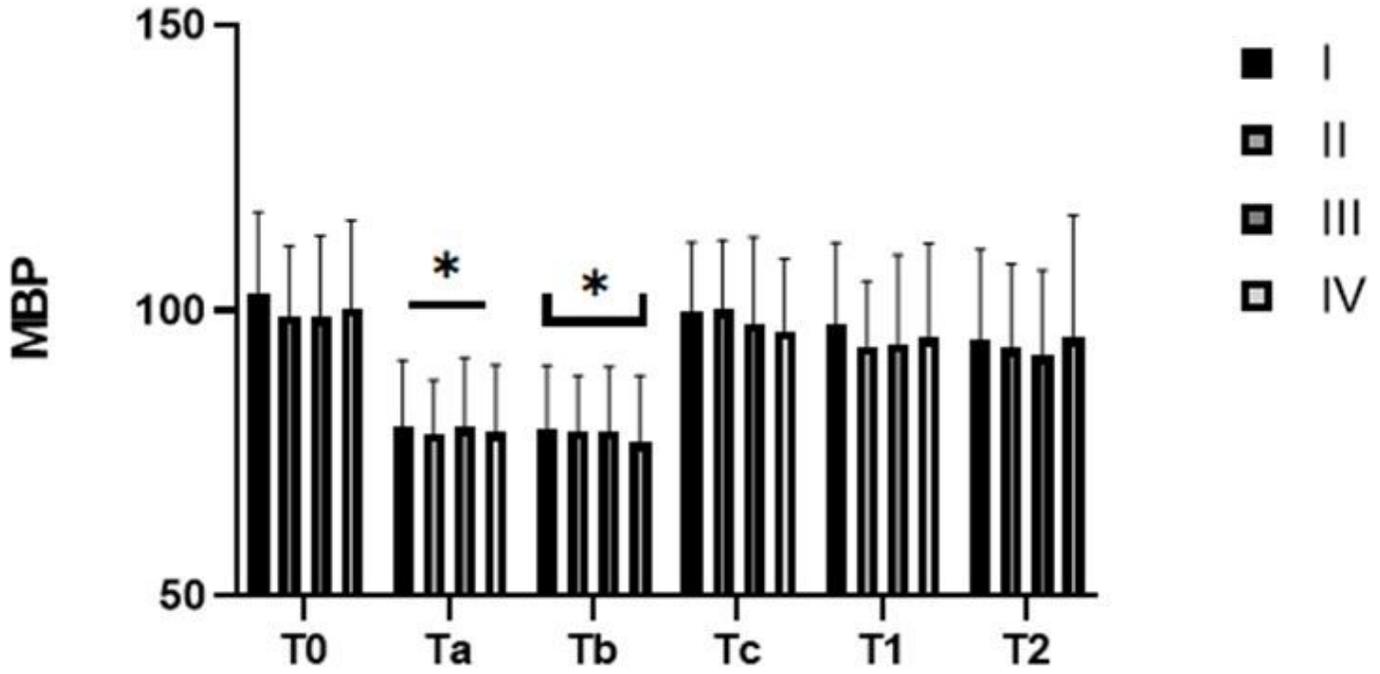


Figure 3

MBP at different timepoints. $\square P < 0.05$, Ta/Tb vs other time in all 4 groups.

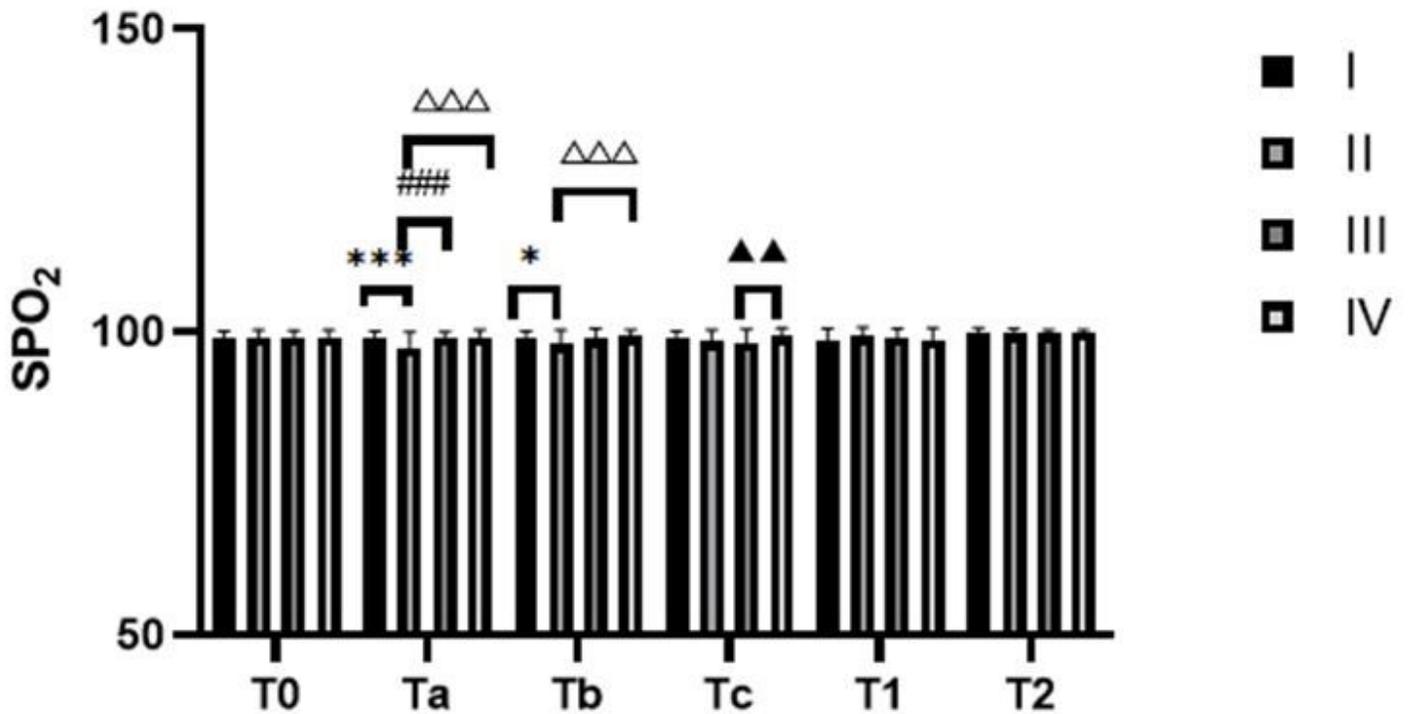


Figure 4

SPO2 at different timepoints. $\square\square\square P < 0.001$ in group II at Ta vs group I, $\#\#\# P < 0.001$ vs group III, $\triangle\triangle\triangle P < 0.001$ vs group IV; $\boxtimes P < 0.05$ in group II at Tb vs group I, $\triangle\triangle\triangle P < 0.001$ vs group IV; $\blacktriangle\blacktriangle P < 0.001$ in group III at Tc vs group IV.

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