



Association of Low Blood Pressure, Low Bispectral Index and Low Minimum Alveolar Concentration of Anaesthetic during Surgery with Postoperative 30-day Mortality: A Systemic Review and Meta-Analysis

Cerrahi Süresince Düşük Kan Basıncı, Düşük Bispektral İndeks ve Anestetiğin Düşük Minimum Alveolar Seviyesinin Postoperatif 30 Günlük Mortalite ile İlişkisi: Sistemik bir Derleme ve Meta-Analiz

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Objective: The triple low state [low mean arterial pressure, low bispectral index (BIS) and a low minimum alveolar concentration (MAC)] fraction of anaesthetic during surgery has been a controversial subject of interest in clinical practise. Previous retrospective studies have produced different conclusions on the association between a triple low state and postoperative 30-day mortality. This study was a systematic review of previous studies on the effects of the triple low state on postoperative 30-day mortality and a meta-analysis with a sample size larger than that of previous studies.

Methods: After searching for relevant articles in the PubMed database as on 27 March 2017, we included studies that compared postoperative 30-day mortality between triple low and non-triple low groups. The identified articles were subjected to an initial screening using keywords 'low bispectral index', 'intraoperative hypotension' and 'low minimum alveolar concentration' according to the PRISMA Flow diagram (2009). After a full-text review, appropriate studies were finally included in our meta-analysis. All statistical analyses were performed using the R programme 3.3.2 and meta packages.

Results: Three retrospective cohort studies were included in the meta-analysis. The total number of subjects in the triple low and non-triple low groups was 29,402 and 17,428, respectively; the sample size was 46,830. We derived a hazard ratio (HR) of 1.09 [95% confidence interval (CI), 1.07–1.11] for the fixed effect model and of 1.30 (95% CI, 1.04–1.07) for the random effect model. In the analysis of heterogeneity among the three studies, $I^2=95\%$ was obtained ($P<0.01$). Thus, the values obtained from the random effect model were used; HR was 1.30 for the triple low group, indicating a 30% increase in the overall 30-day mortality.

Conclusion: The present study demonstrated that patients exposed to the triple low state exhibit higher 30-day mortality rates than those not exposed to the triple low state.

Keywords: Hypotension, bispectral index, anaesthesia

Amaç: Üçlü düşük değerler durumu [cerrahi boyunca düşük ortalama kan basıncı, düşük bispektral indeks (BIS) ve düşük minimum alveolar seviyesi (MAC)] klinik uygulamada tartışılmalı bir konudur. Daha önce yapılmış olan retrospektif çalışmalarda üçlü düşük değerler durumu ile postoperatif 30 günlük mortalite arasındaki ilişki hakkında farklı sonuçlar ortaya koyulmuştur. Bu çalışma üçlü düşük değerler durumunun postoperatif 30 günlük mortalite üzerindeki etkilerini inceleyen önceki çalışmaların sistematik bir derlemesi ve aynı zamanda önceki çalışmalara göre daha geniş bir örneklemle yapılan bir meta-analizdir.

Yöntemler: 27 Mart 2017 itibarıyla PubMed veri tabanında bulunan ilgili makaleleri araştırıldı ve üçlü ve üçlü olmayan düşük değerli grupları postoperatif 30 günlük mortalite açısından karşılaştıran çalışmalar dahil edildi. Belirlenen çalışmalar ilk olarak, PRISMA akış şemasına (2009) göre, 'düşük bispektral indeks', 'intraoperatif hipotansiyon' ve 'düşük minimum alveolar seviyesi' anahtar sözcüklerini kullanarak tarandı. Tüm metin incelendikten sonra, uygun çalışmalar meta-analizimize alındılar. Tüm istatistiksel analizler R 3.3.2 programı ve meta paketler kullanılarak yapıldı.

Bulgular: Meta-analize üç retrospektif kohort çalışma dahil edildi. Üçlü düşük değerler grubu ve üçlü-olmayan düşük değerler grubundaki toplam denek sayısı sırasıyla 29,402 ve 17,428 idi. Örneklem büyüklüğü 46,830 idi. Risk oranı (hazard ratio, HR) sabit etki modeli için 1.09 [%95 güven aralığı (CI), 1,07-1,11] ve rasgele etki modeli için 1.30 (%95 CI, 1,04-1,07) olarak hesaplandı. Üç çalışma arasındaki heterojenlik analizinde $I^2=95\%$ olarak bulundu ($p<0,01$). Böylece, rasgele etki modelinden elde edilen değerler kullanıldı. Üçlü düşük değerler grubu için HR 1.30 olarak bulundu. Bu da toplam 30 günlük mortalitede %30'luk bir artış göstermektedir.

Sonuç: Mevcut çalışma, üçlü düşük değerler durumu olan hastaların, üçlü düşük değerler durumu olmayanlara göre, daha yüksek 30-günlük mortalite oranları sergilediklerini göstermiştir.

Anahtar Sözcükler: Hipotansiyon, bispektral indeks, anestezi

Introduction

Postoperative mortality has been a major subject of interest in clinical practise and a decrease in the same has been the aim of researchers (1, 2). Anaesthesiologists have conducted extensive research for identifying factors associated with postoperative mortality and reported that intraoperative hypotension and a low bispectral index (BIS) independently

and negatively affect postoperative mortality (3-5). Moreover, the risk for stroke (6) and myocardial infarction (7) and 1-year mortality increase (8) when the blood pressure is kept low during surgery. In addition, a low intraoperative BIS of <45 is independent of the deterioration of postoperative prognosis in patients (9). Lastly, a lower BIS and blood pressure in patients receiving a low anaesthetic minimum alveolar concentration (MAC) indicates sensitivity to anaesthesia and a high likelihood of complications. Therefore, a low blood pressure, BIS and MAC should be considered for postoperative prognosis in patients.

In 2012, Sessler et al. (10) proposed the concept of the triple low state (low mean blood pressure (MBP), low BIS and a low MAC fraction of anaesthetic during surgery) and reported an increased duration of hospitalisation and increased 30-day mortality among patients exposed to the triple low state during cardiac surgery. Furthermore, they documented that with an increase in the duration of exposure to the triple low state, the 30-day mortality increases by eight times compared to no exposure; this was an unexpected discovery in the academic world.

However, the results of other studies concerning the triple low state and 30-day mortality have been inconsistent with those reported by Sessler et al. (10) In a study by Kertai et al. (11) that was published in 2014, the 30-day mortality was high for only 30% of all patients in the triple low group, whereas in a study by Willingham et al. (12) that was published in 2015, the 30-day mortality showed no differences between the triple low and non-triple low groups. Willingham et al. (12) claimed that an epiphenomenal relationship, rather than a causal one, may exist between the triple low state and postoperative mortality. This epiphenomenal effect is not a precise causal explanation, but rather a coincidental phenomenon (13). However, certain limitations in the methods employed by Willingham et al. (12) have been highlighted (14), and the effects of the triple low state on postoperative 30-day mortality remain controversial.

The main strength of all retrospective studies that have produced more than three different conclusions regarding triple low and non-triple low groups is the inclusion of a large population that yielded a large dataset for analysis. In the present study, we performed a systematic review of previous studies on the effects of the triple low state on postoperative 30-day mortality and conducted a meta-analysis with a sample size larger than that of previous studies.

Methods

Search strategy and study selection

We followed the PRISMA guideline (2009) for our systematic review (15). After searching for relevant articles in the PubMed database as on 27 March 2017, we included studies that compared postoperative 30-day mortality between triple low and non-triple low groups (reference groups). During the

initial search process, we used the keywords 'low bispectral index', 'intraoperative hypotension' and 'low minimum alveolar concentration'. The identified articles were subjected to an initial screening using the keywords according to the PRISMA Flow diagram (2009). Subsequently, they were screened by their abstracts. All procedures up to and including the second screening process were conducted by an independent medical record technician. After reviewing the abstracts of all articles, articles relevant to our meta-analysis were selected. In total, nine articles were searched after the first database screening process, of which four were selected after screening with keywords. Following a full-text review by the head researcher (T.K Oh), three studies were finally included in our meta-analysis.

Data from the three studies were individually collected by two authors (T.K Oh and I.A. Song). Any disagreement between the two authors was resolved through discussion. In addition, statistical methods used in the three studies were reviewed by a statistician (Y.M. Park), who is also a co-author. The quality of the studies was assessed using the 9-star Newcas-Triple Lowe-Ottawa Scale (The Newcas-Triple Lowe-Ottawa Scale for assessing the quality of non-randomised studies in meta-analyses. Ottawa, Canada: Dept of Epidemiology and Community Medicine, University of Ottawa. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm).

Statistical analysis

We chose the hazard ratio (HR) as the effect size because the primary outcome of this study was the difference in the 30-day mortality between the triple low and non-triple low groups. If the calculated 95% confidence interval (CI) did not include 1, the risk of death in the triple low group was significantly higher than that in the non-triple low group.

The selection of a fixed or random effect model for calculating the average effect size was decided on the assumption that each study was derived from the same population and that the purpose of the analysis was the same. These assumptions were considered based on the characteristics of the study, i.e. the study subjects, intervention methods and study environment. In particular, the fixed effect model was selected if homogeneity statistics were $I < 50\%$ or if the p value was > 0.05 in Q statistics. In all other cases, the random effect model was used. All statistical analyses were performed using the R programme 3.3.2 (<https://www.r-project.org>) and the meta packages.

Results

We included the study by Sessler et al. (10) that was published in 2012, the retrospective cohort study by Kertai et al. (11) that was published in 2014 and the retrospective cohort study using prospectively collected data that was published by Willingham et al. (12) in 2015 in our meta-analysis (Figure 1). The combined total number of subjects in the triple low and reference groups was 29,402 and 17,428, respectively;

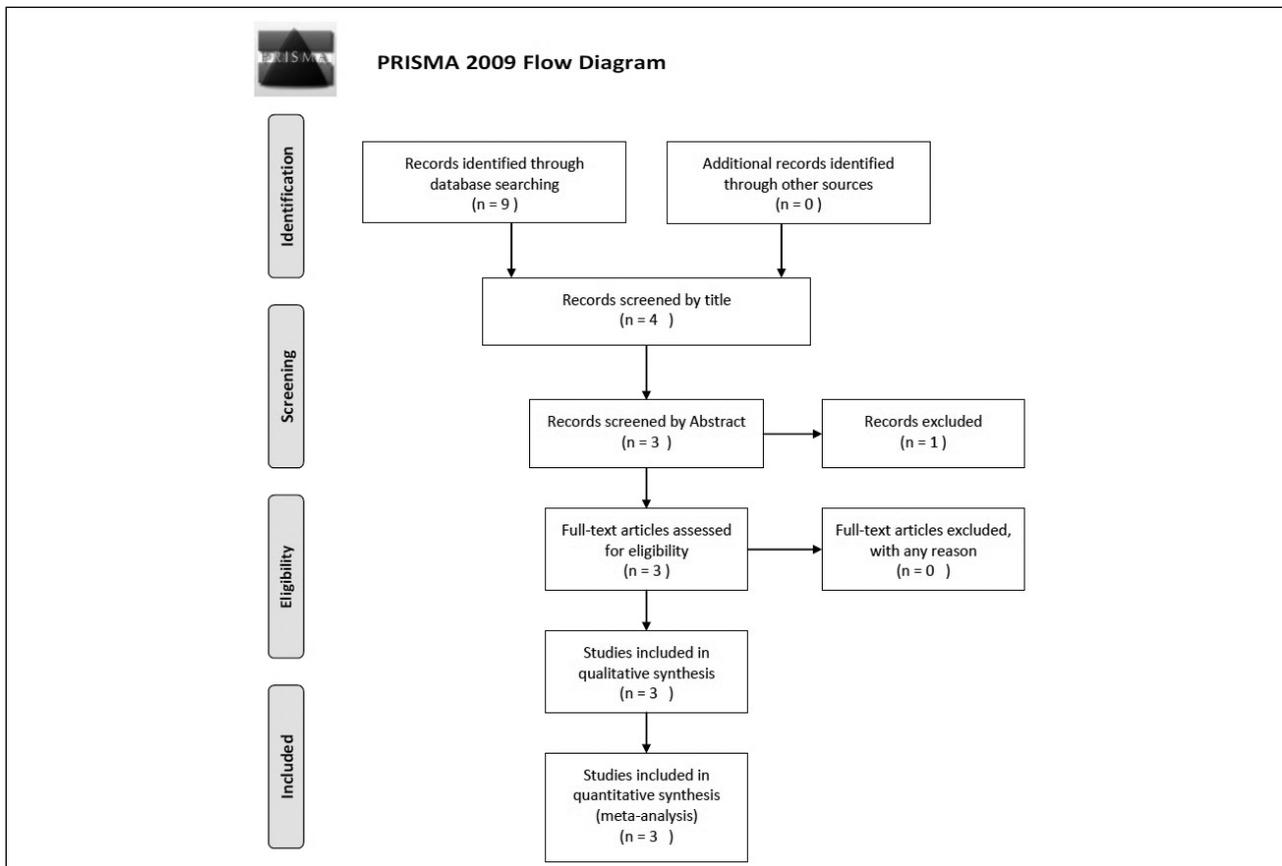


Figure 1. PRISMA 2009 flow diagram

the sample size was 46,830. The characteristics of each study are shown in Table 1. The study by Sessler et al. (10) used data collected from patients at Cleveland Clinic, Ohio, between 6 January 2005 and 31 December 2009. The study by Kertai et al. (11) used data collected from the Duke University Medical Center, Durham, North Carolina, between January 2006 and December 2009. The study by Willingham et al. (12) used data retrospectively collected from three different trials, namely the B-Unaware Trial, International BIS or Anesthetic Gas to Reduce Explicit Recall (BAG-RECALL) trial and the Multicenter AIDS Cohort Study (MACS) (16-18). These three clinical trials were prospective studies conducted at the Washington University, St. Louis, the University of Michigan Health System, Ann Arbor and the University of Chicago and University of Manitoba, Winnipeg, respectively.

In all three studies, the triple low state was defined as MBP of <75 mmHg and BIS of <45. MAC was <0.8 in the studies by Sessler et al. (10) and Willingham et al. (12) and was <0.7 in the study by Kertai et al. (11) Cases involving cardiac surgery in the studies by Sessler et al. (10) and Kertai et al. (11) were excluded from our meta-analysis, whereas cases involving emergency surgery and surgery that did not solely use a single volatile agent in the studies by Sessler et al. (10) and Kertai et al. (11), respectively, were excluded from our meta-analysis. In the study by Willingham et al. (12), patients who had previously undergone surgery requiring a wake-up test; those

with a history of dementia, stroke and/or traumatic brain injury and those for whom the consent forms could not be collected were excluded from our meta-analysis. In addition, patients for whom necessary information was not available were excluded from our meta-analysis.

Sessler et al. (10) and Kertai et al. (11) used the Cleveland Clinic Risk Stratification Index to analyse patient comorbidity (19). Willingham et al. (12) analysed the medical history of each patient. All three studies reported NewcasTriple Lowe-Ottawa scores of 7-8, were high-quality retrospective cohort studies and used a Cox proportional hazards model for statistical analyses. Sessler et al. (10) and Kertai et al. (11) used regression analysis to adjust for patients' baseline characteristics, whereas Willingham et al. (12) used the propensity matching method (20).

30-day overall mortality

HRs for the triple low and non-triple low groups after adjusting for patients' baseline characteristics were 3.96 (95% CI, 2.57-6.10) in the study by Sessler et al. (10), 0.99 (95% CI, 0.92-1.07) in the study by Kertai et al. (11) and 1.09 (95% CI, 1.07-1.11) in the study by Willingham et al. (12) The duration of exposure to the triple low state was not considered during the calculation of HRs in the study by Sessler et al. (10), whereas HRs were calculated every 15 min in the other two studies.

Table 1. Characteristics of three studies

	Sample size	Inclusion	Exclusion	Definition for TL	Statistical method	Newcastle Ottawa score
Sessler et al 2012 (Retrospective cohort study)	9529 (TL: 1495; Reference: 8034)	Non-cardiac Surgery, (age ≥16 years) 6.1.2005–31.12.2009 Cleveland Clinic, Ohio, General Anaesthesia	Emergency surgery incomplete medical record	MBP<75 mmHg BIS<45 MAC<0.8	Cox proportional hazards model Adjustment: Performed using regression analysis	7
Kertai et al 2014 (Retrospective cohort study)	16263 (TL: 10023; Reference: 6240 but missing 563)	Non-cardiac Surgery, (age ≥18 years) 1.2006–12.2009 Duke University Medical Center, Durham, North Carolina, General Anaesthesia	incomplete medical record Not using a single volatile agent	MBP<75 mmHg BIS<45 MAC<0.7	Cox proportional hazards model Adjustment: Performed using regression analysis	7
Willingham et al 2015 (Retrospective cohort study using prospective collected data)	6447 (TL: 3950; Reference: 2497)	Including Cardiac Surgery (age ≥18 years) Using data from three clinical trials (B-Unaware Trial, BAG-RECALL trials and MACS) Washington University in St. Louis, University of Michigan Health System in Ann Arbor and University of Chicago and University of Manitoba in Winnipeg	incomplete medical record Surgery required wake-up test Previous history of dementia or stroke Previous history of traumatic brain injury and unable to obtain informed consent	MBP<75 mmHg BIS<45 MAC<0.8	Cox proportional hazards model Adjustment: Performed using propensity matching method	8

TL: triple low group; MBP: mean blood pressure; BIS: bispectral index; MAC: minimum alveolar concentration

We derived HR of 1.09 (95% CI, 1.07–1.11) for the fixed effect model and that of 1.30 (95% CI, 1.04–1.07) for the random effect model (Figure 2). In the analysis of heterogeneity among the three studies, $I^2=95\%$ was obtained ($p<0.01$), indicating significant variations among the studies. Hence, values obtained from the random effect model were used. In the random effect model, HR was 1.30 for the triple low group, indicating a 30% increase in the overall 30-day mortality.

Discussion

We performed a systematic review and meta-analysis to determine the association between the triple low state and post-operative 30-day mortality by re-using extensive data derived from the three previous studies. The results of the analysis, which included >46,000 patients, showed that compared with the non-triple group, the 30-day mortality increased by 30% in the triple low group. Although variations existed between the three studies, they were adjusted using a ran-

dom effect model. This study is meaningful because it was a meta-analysis that summarised all available evidence on the controversial subject of the triple low state. HRs used in this study are reliable because they were already adjusted in the three studies using a Cox proportional hazard model or the propensity score method.

Each of the three retrospective studies had different limitations. First, as mentioned in an editorial review, the study by Sessler et al. (10) involved the combined use of nitrous oxide and MAC spring agents and did not reflect any changes in anaesthetic techniques over a long period (21). The study by Kertai et al. (11) is unique because a detailed multivariate Cox proportional hazard regression analysis was used for determining 30-day mortality according to the Cleveland risk index scores and underlying diseases. However, similar to previous research, drugs other than inhalation agents were not used in the study because of its retrospective design. In addition, because data collected between 2006 and 2009

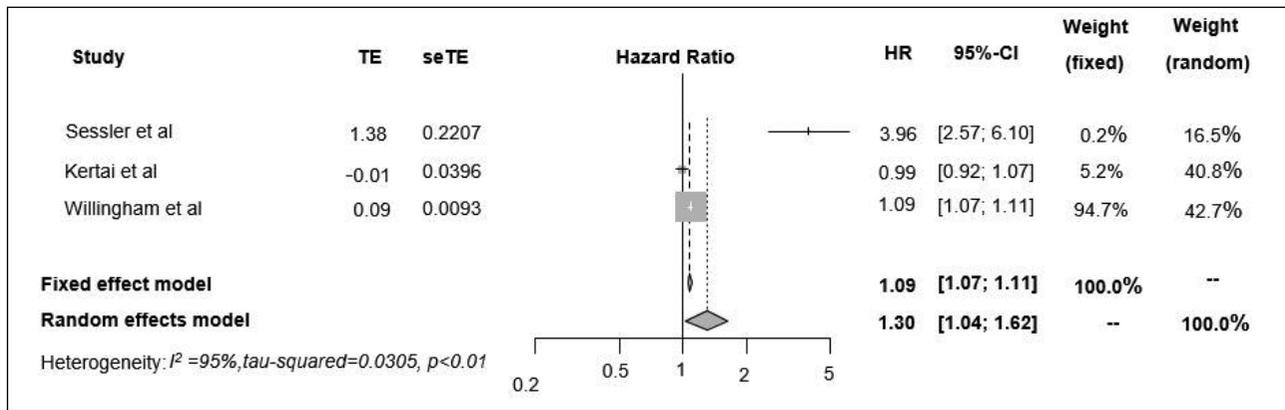


Figure 2. Meta-analysis of hazard ratio between TE and seTE
TE: triple low group; seTE: non-triple low group

were used, the study did not reflect modern anaesthetic techniques. The more recently published study by Willingham et al. (12) included patients who underwent cardiac surgery, unlike previous studies, and used prospectively collected data. Although its strength is that data were collected through a more sophisticated process, its limitations have been highlighted by Pivalizza et al. (14) First, the three randomised controlled trials included in the present analysis used a sample size that was determined through a power analysis related to BIS rather than to the triple low state. Second, it was questioned whether the elimination of >60% subjects in the original triple low group through propensity score matching was statistically appropriate (14).

The first issue to be considered when interpreting the results of this meta-analysis is the relationship between HR and the duration of exposure to the triple low state. Under the general assumption that mortality increases with an increase in the duration of exposure to the triple low state, Kertai et al. (11) and Willingham et al. (12) found HRs that were adjusted every 15 min; these HRs were used in the present meta-analysis. However, in the study by Sessler et al. (10), HRs were not adjusted every 15 min. Rather, they were determined for different durations of exposure for all patients in the triple low group. In the study by Sessler et al. (10), there were 7858, 3536, 1573, 907 and 1555 subjects in the triple low groups with exposure durations of 1–15, 16–30, 31–45, 46–60 and >60 min, respectively. It may be debatable whether HRs determined for this wide range of exposure durations can be compared with HRs adjusted for every 15 min. A meta-analysis in which mortality was analysed according to the duration of exposure to the triple low state would have produced more accurate results; however, this could not be achieved in the current meta-analysis because of limited data.

The next important concern is whether HRs were adjusted for the patients' underlying diseases, which can increase their 30-day mortality, in the three studies. Sessler et al. (10) and Kertai et al. (11) adjusted HRs for the patients' underlying diseases using the Cleveland Clinic Risk Index Score (19).

Kertai et al. (11) demonstrated that, for every one-point increase in the risk index score, the 30-day mortality increased by 70%. Both Sessler et al. (10) and Kertai et al. (11) showed that the American Society of Anesthesiologists (ASA) classification was a main factor that increased 30-day mortality. In contrast, Willingham et al. (12) adjusted HRs for underlying diseases through propensity matching. One strength of the study by Willingham et al. (12) is that it demonstrated a close association of the patients' ASA scores and underlying diseases with 30-day mortality as well as an association of 30-day mortality with each underlying disease. In conclusion, HRs were adjusted for the patients' underlying diseases in the three studies; adjusted HRs were used in our meta-analysis.

The third point to consider is the composition of the sample included in the three studies. While cases of emergency surgery in the study by Sessler et al. (10) were excluded, the study by Kertai et al. (11) showed that an emergency surgery increased 30-day mortality in >60% of all patients. If HRs, which indicate the effects of the triple low state on mortality, calculated after an emergency surgery were included in the study by Sessler et al. (10), the results may have been different. In addition, the inclusion of patients who underwent cardiac surgery in the study by Willingham et al. (12) must have had a huge influence on the results. In general, patients who underwent cardiac surgery are likely to have more underlying diseases than those who did not; furthermore, they are highly likely to be exposed to the triple low state (22). Furthermore, because cardiac surgery using cardiopulmonary bypass results in different haemodynamic states than other elective operations, it is debatable whether a comparison of 30-day mortality among patients who underwent different types of surgery is appropriate.

Finally, with respect to the interpretation of our meta-analysis, the heterogeneity of the control group of the three studies should be considered. Each study used a slightly different definition of a triple low state. Moreover, the inclusion and exclusion criteria involved different ages or surgery types. The difference between the MAC cut-off value of 0.7 in the Kertai et al. (11) study and

of 0.8 in Sessler et al. (10) and Willingham et al. (12) studies resulted in heterogeneity between the control groups in the three studies. In addition, a cut-off point in the three studies for a mean arterial pressure of <75 mmHg and BIS of <45 may not have been appropriate. Alternatively, analyses to determine the reference group should consider the distribution of all vital signs, as performed in a recently published study (23).

In all three studies, the triple low state was defined as MBP of <75 mmHg and BIS of <45. MAC was <0.8 in the studies by Sessler et al. (10) and Willingham et al. (12) and was <0.7 in the study by Kertai et al. (11). Cases of cardiac surgery in the studies by Sessler et al. (10) and Kertai et al. (11) were excluded from our meta-analysis, whereas cases of emergency surgery and surgery that did not solely use single volatile agents in the studies by Sessler et al. (10) and Kertai et al. (11), respectively, were excluded from our meta-analysis. In the study by Willingham et al. (12), patients who had previously undergone surgery requiring a wake-up test; those with a history of dementia, stroke and/or traumatic brain injury and those for whom consent forms could not be collected were excluded. In addition, patients for whom necessary information was not available were excluded from our meta-analysis.

The present study has some limitations. First, as mentioned above, HRs were not adjusted for the duration of exposure to the triple low state using identical methods. If Sessler et al. (10) had adjusted HRs every 15 min, the results of this study may have been more reliable. Second, as mentioned previously, different sample compositions and methods of statistical analyses were used in the three studies. This is a common limitation of all meta-analyses. To adjust for the differences, a random effects model had to be used. Third, because all three studies included in this study were retrospective cohort studies, this meta-analysis bears the inherent limitations of a retrospective study design. Despite these limitations, this study is meaningful in that it conducted a meta-analysis regarding the triple low state using extensive data for >40,000 subjects.

Conclusion

The present study demonstrated that patients exposed to the triple low state exhibit higher 30-day mortality rates than those not exposed. However, because the determined HR was 1.30, which was lower than that for other factors, such as underlying disease and type of surgery, it remains unclear whether the results of this study were obtained because of causal or epiphenomenal effects. Further studies are necessary to clarify our findings.

Peer-review: Externally peer-reviewed.

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