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Evaluation of dexmedetomidine anesthesia-related temperature changes: preliminary retrospective observational study

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KEYWORDS
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Abstract
Introduction and objective: Dexmedetomidine is a potent adrenergic alpha-2 agonist, and analgesic, sedative, anxiolytic and sympatholytic. Given there have been reports of dexmedetomidine associated temperature changes, in which these events have been associated with complications, our objective was to describe both temperature increase and decrease, during the intra and postoperative period (initial 24 hours), and factors associated, in patients who received dexmedetomidine for anesthesia/sedation in the surgical suite.
Method: Retrospective observational study, analyzing charts of patients ≥ 18 years submitted to anesthesia/sedation with dexmedetomidine, between 1/1/2017 and 31/12/2017. Upper temperature threshold was considered ≥ 37.8 °C, and lower, < 35 °C. The association with dexmedetomidine was assessed by the OMS/UMC causality system and by the Naranjo algorithm.
Results: The sample included 42 patients who received dexmedetomidine and whose temperature data were available, with predominance of men 26 (62%), 49.4/16.5 years old (mean/standard deviation), and weight 65/35.8 kg. None of the patients presented intraoperative temperature equal to or above 37.8 °C or below 35 °C. During the postoperative period, one patient presented an increase ≥ 37.8 °C (2.4%) and three, temperature decrease < 35 °C (7%). Surgery/anesthesia time and exposure time to dexmedetomidine were not appropriate linear predictors of maximum temperature. Older age ($p < 0.01$), longer exposure to dexmedetomidine ($p < 0.05$) and shorter surgery time ($p < 0.01$) were significant linear predictors for lower minimum temperature.

Abbreviations: MH, malignant hyperthermia; UMC, Uppsala Monitoring Centre; ICU, Intensive Care Unit; WHO, World Health Organization.

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Conclusions: Increase ≥ 37.8 °C/decrease < 35 °C of temperature possibly associated with dexmedetomidine did not occur in the intraoperative period and had a low frequency during the postoperative period.

Introduction

Dexmedetomidine is an adrenergic alpha-2 agonist and is analgesic/sedative/anxiolytic/sympatholytic.[1] It is frequently used at the Intensive Care Unit (ICU) for mild sedation/ventilation weaning, and at the surgical suite as a sedative/adjuvant, to decrease consumption of opioid/inhalation agents.[1,2] Patients sedated with dexmedetomidine wake up/cooperate when asked and high doses do not result in respiratory depression.[1] The main side effects are hypotension/bradycardia.[1]

Both temperature decrease and increase have been associated with dexmedetomidine.[2–8] Temperature decrease would be due to the agonist action at the central alpha-2 receptor, reducing vasoconstriction/tremor thresholds and physiological responses to increase in body temperature.[1,8,9] Plasma concentration of dexmedetomidine of 0.8 ng.mL^{-1} reduces the tremor threshold to roughly 34 °C.[9] Increase in temperature would result from change in thermoregulation (slight increase in sudoresis threshold) and/or from immunological response (allergic febrile reaction to drug).[2–7,10] Increased temperatures did not correlate to malignant hyperthermia (MH), given there were no signs of hypermetabolism; moreover, patients susceptible to MH anesthetized with dexmedetomidine did not present characteristic presentation/complications.[11,12] Additionally, dexmedetomidine is an option for patients susceptible to MH and allergic to egg protein, contraindicating propofol.[11]

Detailed data on the effect at temperature of dexmedetomidine administered during general anesthesia in adults are scarce. A Cochrane Review[13] on alpha-adrenergics to prevent shivering after general anesthesia emphasizes that it is not possible to establish a relationship between dexmedetomidine and temperature decrease because, of the seven articles analyzed, two did not refer temperature and only one reported the frequency of temperature decrease (44.1%).[14] In the four other articles, there was a decrease in temperature with dexmedetomidine, but two articles did not provide details on the statistical study,[15,16] one article reported no difference between groups without/with dexmedetomidine,[17] and another referred more pronounced decrease in temperature in the group with dexmedetomidine, only during the postoperative period.[18] Additionally, a retrospective study on the effect of dexmedetomidine on postoperative inflammation after percutaneous nephrolithotomy showed a significant decrease in fever/systemic inflammatory response syndrome.[19] Finkel (2007) reported decrease in temperature while using dexmedetomidine at the ICU on neonates.[8]

Regarding temperature increase associated with dexmedetomidine, data come from ICU studies[2–5,7] or experimental models, in addition to a report on anesthesia of a child with suspected MH in the absence of triggering agents.[6] Dogs anesthetized with sevoflurane/opioid versus sevoflurane/dexmedetomidine presented both increase and decrease in temperature in both groups, but with no significant difference, both in the intra and postoperative periods.[20] In rodents, temperature was significantly lower with isoflurane than with dexmedetomidine/ketamine/midazolam and more animals had temperature decrease with isoflurane, leading the authors to propose that dexmedetomidine could protect against skin heat loss by peripheral vasoconstriction, and preserve central temperature by central blood redistribution.[21]

Thus, there is a gap in detailed studies on the effects of dexmedetomidine on temperature during the intra/postoperative period.

Objective

To describe both increase and decrease in intra/postoperative temperature variation (initial 24 hours), and factors associated, in patients receiving dexmedetomidine for anesthesia/sedation at the surgical suite.

Methods

The study was performed in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsink), approved by the Ethics and Research Committee (CAAE 08688512.0.0000.5505; 115.960, 05/OCT/2012), and given it was a retrospective study, informed consent was waived. Following STROBE guidelines, an observational retrospective study was performed at a tertiary hospital, on patients who received intraoperative dexmedetomidine at the surgical suite during the 01/JAN/2017-31/DEC/2017 period.

First, an author revised the electronic database of anesthesia/medical records of all patients included, registering maximum/minimum temperature/temperature amplitude during the intraoperative/initial 24 hours of the postoperative period. Intraoperative data were collected from the anesthesia record and postoperative data from nursing notes. The 24-h limit was based on detection of temperature increase, of adult ICU patients, up to 24 hours after dexmedetomidine, and normothermia up to 12 hours after discontinuation.[2] Inclusion criteria were using dexmedetomidine and availability of temperature control data. Exclusion criteria were age below 18 years due to the specificity of thermogenesis in children, with production of heat by brown fat, and larger body surface in relation to mass.[22]

The following data were collected from charts: demographics (age/gender), height-weight, history of current condition and surgical proposal, previous diseases, medications being used, type of anesthesia/sedation, anesthetic drugs used, beginning/end of procedures (anesthesia/sedation, surgery), incidents/complications from the beginning of anesthesia/sedation to discharge from post-anesthesia recovery, maximum and minimum temperature data. Daytime temperature varies between 36.5–37.5 °C and values < 36 °C and > 38 °C mark points in which thermoregulation is compromised and/or surpassed by changes in environment temperature/thermogenesis.[22] To amplify any possible association between dexmedetomidine and change in temperature, increase in temperature ≥ 37.8 °C and decrease in temperature < 35 °C were considered as limits. Temperature ≥ 37.8 °C was adopted to define acceptable limit for fever, while 34.6 °C was the temperature that induced thermoregulatory response of peripheral vasoconstriction in normal individuals exposed to cooling.[9,23]

In order to better assess the relationship between dexmedetomidine and change in temperature, possible infectious/non-infectious causes of temperature increase were considered. The association between dexmedetomidine and temperature increase/decrease was assessed by two algorithms: World Health Organization (WHO)/Uppsala Monitoring Centre (UMC) system for standardized case causality assessment and Naranjo algorithm.[24,25] WHO-UMC criteria compare the drug-effect relationship in question, with a table of pre-defined statements and six categories: non-classifiable, not classified, unlikely, possible, likely, and defined (Supplementary Material: Table 1).[24] The Naranjo scale is a point system with a questionnaire (0–13 points) that classifies the drug-effect relationship in four categories: doubtful (0), possible (1–4), probable (5–8) and definite (≥ 9) (Supplementary Material: Table 2).[25] Two evaluation methods were used because the level of causality has been reported as different among several pharmacovigilance algorithms.[2]

To calculate the sample size, we chose the increase in temperature variable because it is less studied/frequent. Increase in temperature with dexmedetomidine was considered as occurring in up to 6.5% of patients in previous studies on adults in the ICU[26]; thus, in order to replicate this proportion with a maximum estimation error of 5% and 80% level of confidence, a sample of 40 patients would suffice (calculation based on simple random sample without replacement). Categorical data were described as absolute (n) and relative (%) frequency, and continuous and semi-continuous gaussian data, as mean and standard deviation. Data were checked as to normality by the K-S distance test. Non-paired *t*-test was used to compare independent samples. Correlations were calculated/tested by the Pearson test. To better check the relationship between use of dexmedetomidine and patient temperature, linear regressions were performed including variables that presented a significant correlation on the Pearson test. Based on the assumption that time of dexmedetomidine and patient temperature correlate in a linear relationship, linear regression was performed to determine how much variation in patient temperatures would be explained by time of use of dexmedetomidine, surgery time and age in years, separately. Values of $p < 0.05$ were considered significant.

Results

The study included 42 patients who received dexmedetomidine during the intraoperative period and with temperature control available, 49.4/16.5 years old (mean/standard deviation; variation 19–81 years), 65/35.8 kg (data available for 39 patients; variation 42–115 Kg), and 26 (62%) men and 16 women (38%). Seven patients who received intraoperative dexmedetomidine were excluded due to unavailable temperature control data.

Two patients (4.76%) had baseline infectious conditions (infectious source surgically approached at pulmonary metastases and pulmonary infection). None of the patients were septic. Awake intubations were performed in 8 patients (19%). Elective procedures prevailed (36) over urgencies (6). Central nervous system surgeries were more frequent (13), followed by head/neck (8), gastrointestinal (5), orthopedic (4), ENT (3), vascular (2), urology (2), plastic (2), ophthalmology (1), gynecology (1), and heart (1). The abdominal cavity was opened in three surgeries (7.14%), and none of the thoracic cavity. None of the patients used extracorporeal circulation or had burns. One patient died at the hospital 21 days after the procedure. Mean time to discharge after surgical procedure was 3.46/3.29 days (variation 1–14 days).

Dexmedetomidine was used as sedation in nine cases (21%) and as anesthesia adjuvant in the other 33 (25 also received isoflurane, opioid and propofol; seven, opioid and propofol; and one, local anesthetic). As adjuvant, dexmedetomidine was used alone in 76.2%, associated with clonidine in 7.1%, and to ketamine in 16.7% of cases. Dexmedetomidine was used for 202.73/150.9 minutes (range 30–660 minutes), at the dose of 0.47/0.09 micrograms.$kg^{-1}.h^{-1}$ (range 0.3–1).

Temperatures were measured during anesthesia/sedation with an esophageal thermometer and, at the postoperative period, with an axillary thermometer. All patients used thermal blankets adjusted to 38 °C for warming after general anesthesia induction or beginning of sedation. None of the patients were cooled down. Among maximum temperatures, highest was 37.9 °C, and lowest, 35.6 °C (mean 36.7/0.54 °C) (Fig. 1). Among minimum temperatures, highest was 36.6 °C and lowest, 34.6 °C (mean 35.6/0.56 °C). The widest temperature range (maximum temperature minus minimum temperature) on the same patient was 2.9 °C, and the lowest, 1 °C (mean 1.03/0.61 °C).

None of the patients presented temperature increase ≥ 37.8 °C during the intraoperative period, and only one patient presented temperature increase ≥ 37.8 °C in the postoperative period. The correlation between increase in temperature ≥ 37.8 °C and use of dexmedetomidine for this patient was considered as possible by the WHO-UMC causality system, and by the Naranjo algorithm (Table 1).

None of the patients had a temperature < 35 °C during the intraoperative period, but three patients (7%) did in the postoperative. For these patients, the correlation between temperature < 35 °C and using dexmedetomidine was considered as possible by the WHO-UMC causality system for three,

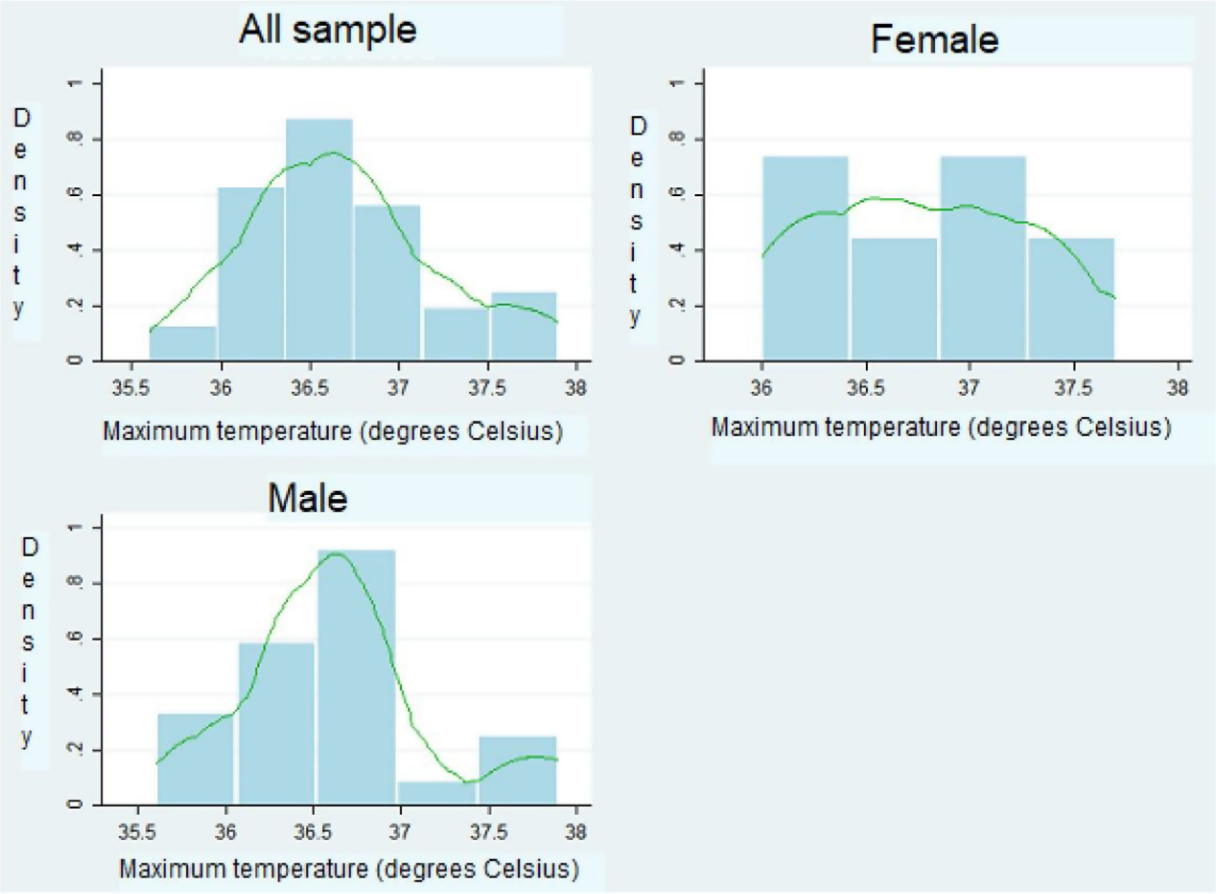

Figure 1 Histogram of distribution of maximum temperature for the entire sample and by gender.

Table 1 Patient with temperature ≥ 37.8 °C or < 35 °C in postoperative period.

Patient	Change	Temp. value	Who-UMC	Naranjo[a]			
				Classification	Conclusive reports previous to current reaction (yes: +1, no: 0)	Adverse event emerged after medication (yes: +2; no: −1)	There were other possible causes for reaction (yes: −1, no: +2)
1	Temp. ≥37.8 °C	37.9	Possible	Possible[b] 2 points	Yes (+1)	Yes (+2)	Yes (-1): infection
2	Temp. <35 °C	34.8	Possible	Possible[b] 2 points	Yes (+1)	Yes (+2)	Yes (-1): inhalation anesthetic/ propofol/opioid
3	Temp. <35 °C	34.6	Possible	Probable[c] 5 points	Yes (+1)	Yes (+2)	No (+2)
4	Temp. <35 °C	34.8	Possible	Possible[b] 2 points	Yes (+1)	Yes (+2)	Yes (-1): inhalation anesthetic/ propofol/opioid

Temp., Temperature; WHO-UMC, World Health Organization (WHO)/Uppsala Monitoring Centre (UMC) system for standardized case causality assessment: ''Possible'' on Who-UMC is equivalent to ''event or abnormal lab test with reasonable time relationship with drug ingestion, but also can be explained by other conditions or medications, and at sites where information of medication withdrawal may be absent or not very clear''.

[a] Naranjo: only questions that comprise point score were listed; questions that did not have points were not listed, that is, value was zero.

[b] ''Possible'' on the Naranjo scale is equivalent to 1–4 points.

[c] ''Probable'' on the Naranjo scale is equivalent to 5–8 points.

and by the Naranjo algorithm, as possible for two and likely for one (Table 1). The relationship between temperature decreases and dexmedetomidine was classified as possible when there were other medications/scenarios that could explain the increase/decrease in temperature. Additionally, none of the patients presented a temperature < 36 °C during the intraoperative period, but 20 patients presented a temperature of 35–35.9 °C in the initial 24 postoperative hours.

There was no difference in maximum temperature between females (36.8/0.5 °C) and males (36.6/0.5 °C) (non-paired *t*-test, $p = 0.15$) (Fig. 1), nor between patients aged up to 49 years (36.8/0.1 °C) and those above 50 years or more (36.6/0.1 °C) (non-paired *t*-test, $p = 0.19$). Likewise, there was no difference between minimum temperature between sexes nor between patients above/below 50 years. There was no significant difference in minimum (respectively 35.49/0.16 °C vs. 35.68/0.93 °C; $p = 0.19$, non-paired *t*-test) or maximum temperature (36.64/0.12 °C vs. 36.68/0.1 °C; $p = 0.33$, unpaired *t*-test) between the group that only received dexmedetomidine (n = 9) and the group in which dexmedetomidine was associated with other anesthetics (n = 33).

The period of use of dexmedetomidine presented a low positive correlation with maximum temperature (correlation coefficient $r = 0.3$; $p < 0.05$; Pearson correlation), and high correlation with surgical time ($r = 0.7$; $p < 0.05$; Pearson correlation) (Fig. 2; Table 2). Maximum temperature presented a low positive correlation with surgery time ($r = 0.3$; $p < 0.05$; Pearson correlation) and with minimum temperature ($r = 0.3$; $p < 0.05$; Pearson correlation), but a high positive correlation with temperature amplitude ($r = 0.7$; $p < 0.05$; Pearson correlation) (Table 2). Minimum temperature presented a low positive correlation with surgery time ($r = 0.3$; $p < 0.05$; Pearson correlation), low negative correlation with age ($r = 0.3$; $p < 0.05$; Pearson correlation) and high negative correlation with temperature amplitude ($r = 0.7$; $p < 0.05$; Pearson correlation) (Fig. 3; Table 2).

Linear regression of temperature as a function of time using dexmedetomidine, surgery time and age (Table 3) presented a variance inflation rate (VIF) < 10 (1.04–2.44), excluding the possibility of collinearity. Analyzing first the regression in which the variable explained is maximum temperature, Table 3 shows that both surgery time and dexmedetomidine time and age did not have a statistically significant relation with maximum patient temperature. In turn, when analyzing minimum temperature of patients, time using dexmedetomidine was observed to have a negative relationship with minimum patient temperature (the more time using dexmedetomidine, lower minimum patient temperature). A similar relationship was found for age, that is, older individuals had lower temperatures. In turn, the longer surgery time, higher the minimum temperature. There was no statistically significant relationship of the variable dexmedetomidine alone/associated with minimum/maximum temperature.

Discussion

We detected both temperature > 37.8 °C and < 35 °C in less than 10% of the sample. In the present statistical modeling, temperature decrease could, independently, be due to both older age and more time using dexmedetomidine and longer surgery time. On the other hand, increase in temperature apparently depends on joint action of dexmedetomidine and surgery time.

Sessler (2008) underscored that individuals without thermoregulation problems would not present decrease in temperature only due to factors such as low temperature of the operating room, exposure of cavities, hemorrhage/transfusion, previous conditions (ASA 3–4), malnutrition, neuropathies and older age.[10,22] Decrease in intraoperative temperature would imply in inhibition of thermoregulation by anesthetics such as dexmedetomidine, with consequent lower threshold for tremor and vasoconstriction, loss of heat from central compartment to periphery by vasodilation, and up to 30% decrease in metabolism.[10,22] This would explain our findings of lower minimum temperatures associated with longer exposure time to dexmedetomidine when we isolated the effects of surgery time and age.[9] Additionally, mechanisms that predisposed to temperature decrease during anesthesia apparently would stand out in relation to those that would cause temperature increase by dexmedetomidine, a different scenario from the studies performed at ICU. Prevention of temperature decrease is warranted by associated risks, such as coagulopathy (platelet/coagulation factors dysfunction), delay in anesthesia recovery, cardiac complications (increased noradrenaline, arterial hypertension, and tachycardia), shift in the hemoglobin dissociation curve to the left, and higher incidence of surgical wound infection.[10]

A series of 200 ICU patients on dexmedetomidine detected a temperature increase of nine, on average after six hours (range 4–10 hours) from initial dexmedetomidine at a mean dose of 1.0 $mcg.kg^{-1}.\ h^{-1}$ (0.8–1.3), with a temperature decrease after discontinuation of dexmedetomidine to $\leq$ 38.5 °C, on average in 3 hours (1–8), and to $\leq$ 38.0 °C after 4 hours (3–9).[2] Authors have suggested that dexmedetomidine could be associated with occurrence of clinically relevant temperature increases.[2] Grayson et al. showed a significant correlation between using dexmedetomidine at the ICU and increased temperatures, mainly in the postoperative period of cardiac procedures and of the obese.[27] The same correlation was not found in the present study on intraoperative use of the medication, although, in agreement with Grayson et al., we also detected maximum temperature increase associated with long exposure time to dexmedetomidine.[27]

Malignant Hyperthermia (MH) and Neuroleptic Malignant Syndrome (NMS) should be considered as part of the differential diagnosis in any fever of unknown origin. However, temperature increase associated with dexmedetomidine is different because high creatinoquinase is not always present, and symptoms tend to stop after its interruption.[27] Beside external factors that can increase temperature, infection can explain temperature increase, as is the case of the patient with postoperative fever and infection in cervical metastases. The relationship between temperature increases and dexmedetomidine was classified as possible in this patient, because there is another disease that could explain temperature increase. Increased temperature due to drugs is a challenge for diagnosis, that frequently is only made by exclusion, with time/resources spent in cul-

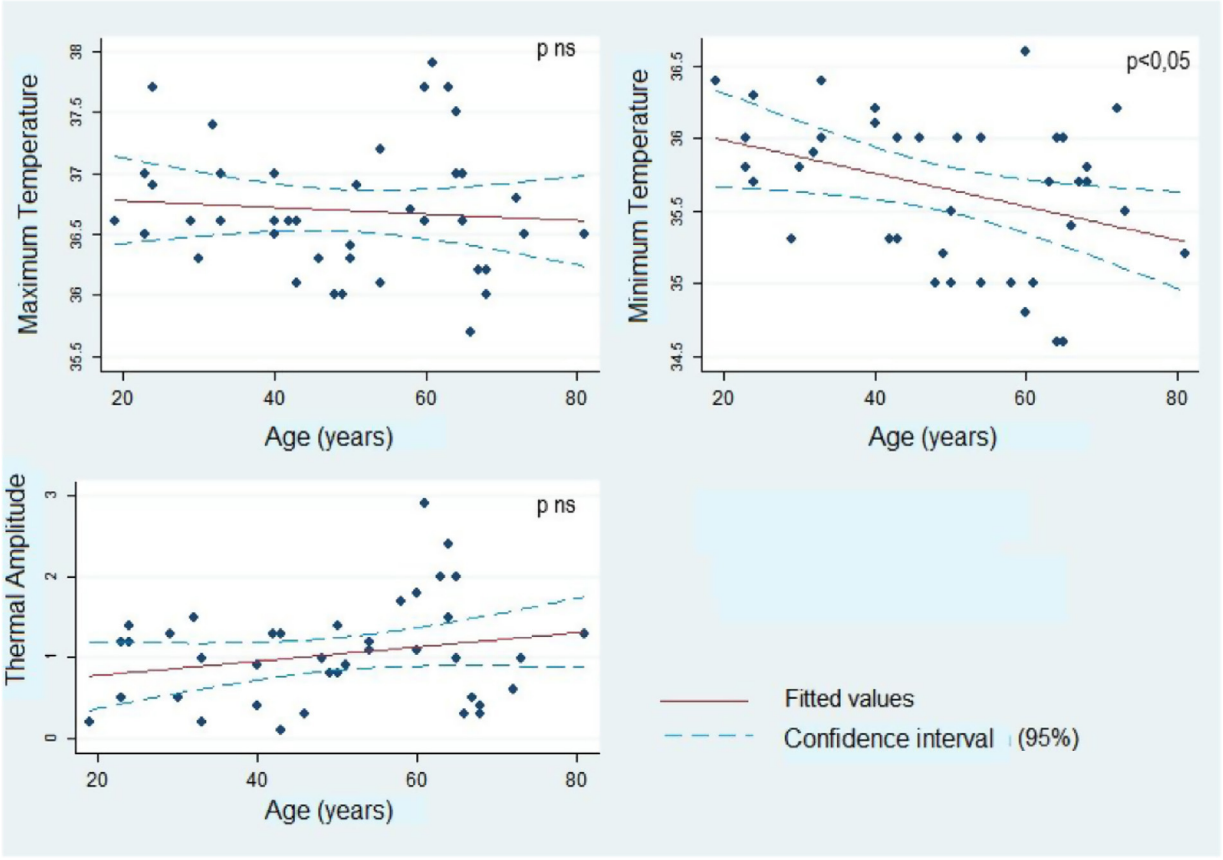

Figure 2 Dispersion and linear prediction of maximum temperature, minimum temperature, and temperature amplitude, by age.

Table 2 Pearson correlation matrix of variables of interest (values refer to correlation coefficients *r*).

Correlation	Maximum T.	Minimum T.	Temperature amplitude	Age	Surgery time	Dexmedetomidine use time	Concentration of dexmedetomidine
Maximum T.	1	–	–	–	–	–	
Minimum T.	0.3310[b]	1	–	–	–	–	
Temperature amplitude	0.5964[c]	0.5600[c]	1	–	–	–	
Age	-0.0848	-0.3654[b]	0.2291	1	–	–	
Surgery time	0.3702[b]	0.3344[b]	0.0405	0.0498	1	–	
Dexmedetomidine use time	0.3699[b]	0.1185	0.2239	-0.042	0.7089[c]	1	
Concentration of dexmedetomidine	-0.0935	0.1855	-0.2291	-0.3205	-0.079	-0.2372	1

T., Temperature.
[b] $p < 0.05$.
[c] $p < 0.01$.

tures/antibiotics; with a subjacent infection, the diagnosis becomes even more difficult and sometimes is not made, even during follow-up.

Measures to minimize temperature decrease in anesthesia/sedation, such as thermal blankets, are confounding factors in the present study, by limiting the occurrence of intraoperative temperature decrease. Longer surgery time associated with higher minimum/maximum temperatures suggest that using a blanket may be a prevailing factor in this relationship. Another confounding factor in the present study was using distinct temperature measuring methods, esophageal at the surgical suite and skin in the initial 24 postoperative hours; thus, despite the reliability of intraoperative temperatures, they can be underestimated in the postoperative period. Skin temperature has a low correspondence with esophageal temperature, more efficient because it is closer to central temperature.[28] Lack of data on temperature measurements in all patients who used dexmedetomidine limited our work by decreasing the number of cases analyzed. Additionally, this study has limita-

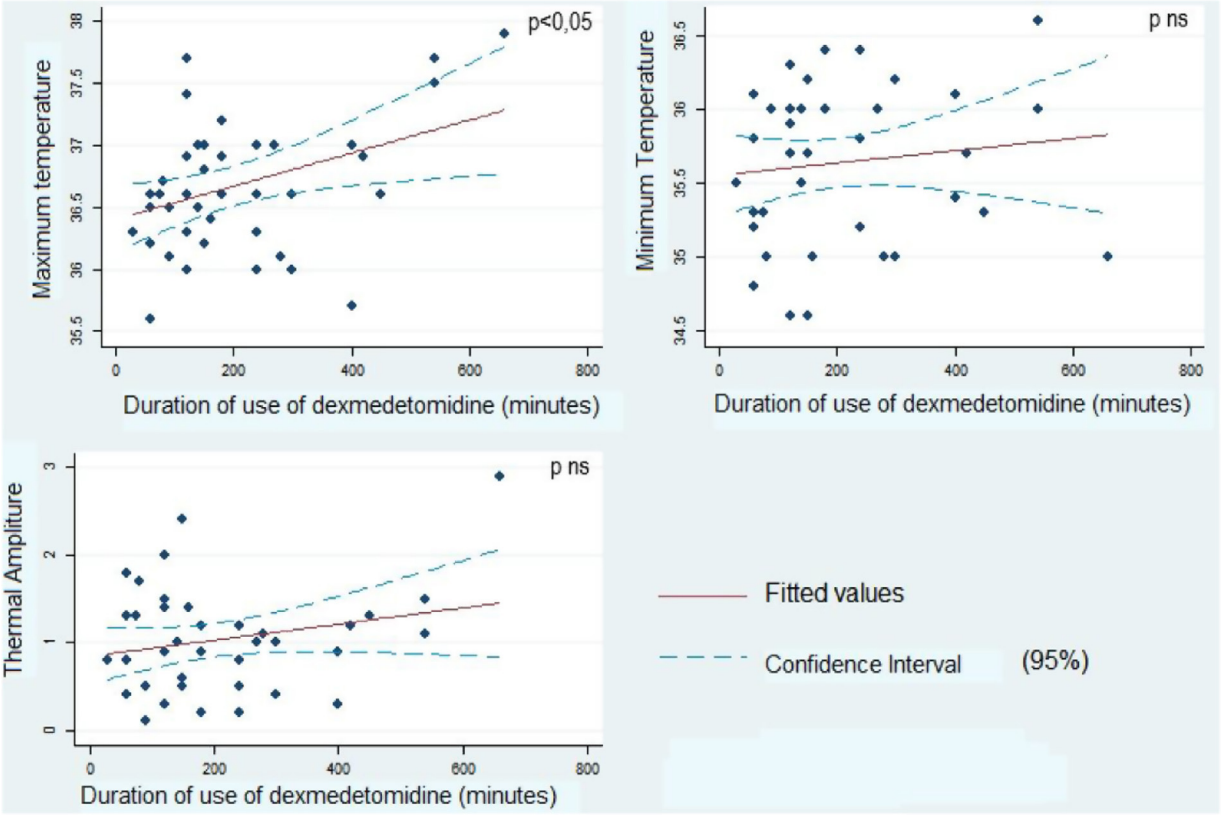

Figure 3 Dispersion and linear prediction of maximum temperature, minimum temperature, and temperature amplitude, by time using dexmetedomidine.

Table 3 Linear regression of maximum temperature and minimum temperature in relation to dexmedetomidine use time, surgical time, age (standard deviation between parentheses). Additionally, control was performed by variable dexmedetomidine alone or associated to other anesthetics.

Variables	Temperature (degrees Celsius)	
	Maximum	Minimum
Dexmedetomidine use time (minutes)	0.0001 (0.00079)	-0.0014[a] (0.0007)
Surgical Time (minutes)	0.00143 (0.00067)	0.0018[b] (0.0006)
Age (years)	-0.005 (0.0051)	-0.0139[b] (0.00454)
Single/Associated Dexmedetomidine	0.1694 (0.663)	-0.471 (0.591)
Single/Associated Dexmedetomidine and Dexmedetomidine use time (minutes)	0.0041(0.005)	0.0036 (0.004)
Single/Associated Dexmedetomidine and Surgical Time (minutes)	-0.0029 (0.0024)	0.0004 (0.0021)
R^2	**0.23**	**0.36**

[a] $p < 0.05$.
[b] $p < 0.01$.

tions due to its retrospective method, with a heterogeneous sample as to variables such as type of surgical procedure, without monitoring/anesthesia protocol established previously, with anesthesia/sedation performed/registered by different anesthesiologists, and without room temperature control. In order to better determine the cause-effect relationship, it would be important to perform future prospective studies, controlling all variables. However, information from the present study is important for awareness on the topic and to provide data for prospective studies to base themselves on, mainly to calculate sample size.

The major temperature variation found for patients in our study can be related to a wider interval between thresholds for response to cold/heat which is inducted by anesthetics, ranging from 0.2–0.4 °C to 2–4 °C.[22] Temperature variations with dexmedetomidine could lead to considering monitoring temperature during its use. The Federal Medical Council recommends determining temperature and the means to assure normothermia, for procedures above 60 minutes and, regardless of procedure duration in high-risk scenarios (premature, newborn, previous history of/risk of MH and NMS).[29]

Although maximum temperature presented a significant positive correlation with surgical time and exposure to dexmedetomidine, these variables were not significant on the linear regression, indicating that they are not appropriate independent linear predictors of maximum temperature. On the other hand, age, surgery time and exposure time to dexmedetomidine were significant linear predictors for minimum temperature, in that older age and longer time of exposure to dexmedetomidine related to lower minimum temperatures, while longer surgery time was linked to higher minimum temperatures. These results should be seen parsimoniously, because it is not possible to infer on causality, and because the magnitude/direction of these effects can vary when controlling for other characteristics of patients/procedures. Moreover, the number of observations was low, with little variability, and the coefficients found were low, indicating a weak relationship among variables.

The significant relationship between older age and lower maximum/minimum temperature is explained by less efficient central thermoregulation for the elderly than for young adults, because of decreased baseline metabolism, muscular mass, tremors, sensitivity to cold and vasoconstrictor response.[10,30] The vasoconstriction threshold from 60–80 years falls 1 °C in comparison to 30–50 years.[22] Dexmedetomidine use may need more care in the elderly because of exacerbation of the trend to decrease temperature, especially in the postoperative period, when the patient is not subject to temperature monitorig and control implemented by the anesthesiologist.

Conclusion

None of the patients presented increase ≥ 37.8 °C/decrease < 35 °C in intraoperative temperatures. Increase ≥ 37.8 °C/decrease < 35 °C in postoperative temperatures possibly associated with dexmedetomidine (OMS/ UMC causality system, Naranjo algorithm) presented a low frequency.

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Author's contribution

Felipe Aparecido Ferreira da Cruz: Data acquisition, data analysis and interpretation, preparation of manuscript, final approval of version submitted.

Luiz Fernando dos Reis Falcão: Study conception and design, critical revision of manuscript due to important intellectual content, final approval of version submitted.

José Luiz Gomes do Amaral: Study conception and design, critical revision of manuscript due to important intellectual content, final approval of version submitted.

Helga Cristina Almeida da Silva: Study conception and design, data analysis and interpretation, preparation of manuscript, final approval of version submitted.

Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.bjane.2021.02.062.

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