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Dexmedetomidine for attenuating haemodynamic response to intubation stimuli in morbidly obese patients anaesthetised using low-opioid technique: comparison with fentanyl-based general anaesthesia

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Abstract

Background: Anaesthesiologists are facing the problem of an increasing population of morbidly obese patients. In order to minimize the risk of opioid-induced postoperative respiratory failure, the intraoperative administration of opioids should be reduced or replaced with other drugs. The purpose of this study was to compare haemodynamic response elicited by intubation in morbidly obese patients between two variants of anaesthesia induction: fentanyl-based or low-opioid using dexmedetomidine.

Methods: Forty-two morbidly obese patients scheduled for bariatric surgery were randomly assigned to two groups: low-opioid using dexmedetomidine (DEX) or fentanyl-based (FNT) anaesthesia. Patients were premedicated with 100 μg of fentanyl i.v. In the DEX group, a 10 minute infusion of a loading dose of 200 μg of dexmedetomidine was started. In the FNT group, 2 mg of intravenous midazolam was given. Thereafter, propofol was used in both groups. In the FNT group, patients received a dose of fentanyl up to 5 μg kg^{-1} of ideal body weight. Following administration of rocuronium, laryngoscopy and tracheal intubation were performed. Haemodynamic parameters, including systolic (SBP), diastolic (DBP) and mean arterial (MAP) blood pressure, as well as heart rate (HR), were recorded before and after intubation. Patients who were not intubated at first attempt were excluded from the study.

Results: Data from 33 patients were analysed. There were no statistically significant differences between the DEX and FNT groups regarding demographic data. Haemodynamic response to intubation was defined as mean change (d) in values of analysed parameters that occurred during intubation. The following differences were observed: dSBP FNT +11.6 mm Hg vs. DEX +0.4 mm Hg ($P = 0.15$); dDBP FNT +3.7 mm Hg vs. DEX +3.5 mm Hg ($P = 0.98$); dMAP FNT +8.6 mm Hg vs. DEX +1.4 mm Hg ($P = 0.36$); dHR FNT +2 beats min^{-1} vs. DEX −1 beat min^{-1} ($P = 0.30$). None of these comparisons yielded significant differences.

Conclusions: The study revealed no advantage of fentanyl over low opioid dexmedetomidine-based induction of general anaesthesia in attenuating cardiovascular response to intubation in morbidly obese patients.

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Key words: dexmedetomidine, fentanyl, intubation, obesity

Obesity is becoming a major epidemiological problem, with the number of obese persons doubling since 1980, and reaching over 600 million in 2014. In Poland, the population of obese persons increased by 9% between 2010–2014 [1]. Treatment of obesity and its complications has become a significant challenge in modern medicine, and particularly in anaesthesiology. Apart from the acknowledged obesity complications such as insulin-resistance, type 2 diabetes, cardiovascular disease, hormonal imbalance, glomerulopathy or neoplasia, other disorders should also be mentioned in this patient population since they concern the respiratory system and might be of particular importance for anaesthesiological practice. These include obstructive sleep apnoea, hypoventilation syndrome or postoperative atelectasis [2].

Obese patients are prone to develop adverse respiratory events, referred to as critical respiratory events (CRE), in the postoperative period following general anaesthesia [3]. For safety reasons, the need to adjust general anaesthetic protocols for this patient population has been acknowledged. According to current concepts, patients at particular risk of developing respiratory complications during general anaesthesia include obese persons, the elderly and children. In these patient groups, the administration of non-opioid agents (clonidine, ketamine or dexmedetomidine) is suggested instead of opioids [4].

The standard algorithm of general anaesthesia includes opioid administration for intraoperative analgesia as opioids provide a good haemodynamic control in cases of strong pain stimulation. Laryngoscopy and tracheal intubation are believed to be among the strongest pain stimuli, comparable with peritoneal incision. For the intravenous induction of combination anaesthesia, propofol, an opioid (fentanyl, sufentanyl or remifentanil) and a benzodiazepine (such as midazolam) are chosen. Opioids may potentially be replaced by dexmedetomidine, an alpha-2 receptor agonist having sedative, hypnotic, sympathicolytic and analgetic properties [5]. In Poland, this agent is registered for the sedation of patients treated in intensive care units (ICU).

The aim of the presented prospective randomized study was to evaluate if dexmedetomidine may provide adequate analgesia during tracheal intubation, and whether may become an alternative to opioids.

METHODS

Ethical approval for the study was obtained from the local commmittee at the Medical University in Lódź (no. RNN/60/16/KE). Fourty-two obese patients, with BMI (Body Mass Index) > 40 kg m^{-2}, deemed qualified for the laparoscopic procedure of gastric banding, were randomised to two groups. In one group, anaesthesia was introduced with an opioid (fentanyl, FNT), in full analgetic dose. In the other group, dexmedetomidine (DEX) was used for induction.

All patients were premedicated with 100 µg intravenous fentanyl. Thereafter, patients in the FNT group received 2 mg intravenous midazolam, while the subjects in the DEX group were given 200 µg dexmedetomidine in an intravenous infusion over 10 minutes [6]. After preoxygenation, all patients were administered intravenous propofol titrated so as to obtain the bispectral index (BIS) values of < 60. Then, fentanyl was used in the FNT group so as the total administered drug amount, including premedication, reached maximally the analgetic dose of 5 µg kg^{-1} ideal body weight (IBW). For muscle relaxation, rocuronium at 0.6 mg kg^{-1} IBW was given. Intubation was attempted when total (100%) suppression of neuromuscular transmission could be confirmed, as verified by a train-of-four (TOF) stimulation assay using the TOF-Watch device.

Table 1. Demographical data in both patient groups. Values are expressed as mean ± SD

	DEX	FNT	*P*-value
Age (years)	39.6 ± 10.6	37.1 ± 8.8	0.014
Body height (cm)	171.2 ± 9.3	170.9 ± 9.6	0.39
Body mass (kg)	129.1 ± 19.8	128.9 ± 22.7	0.34
BMI (kg m^{-2})	44.0 ± 5.7	44.0 ± 3.6	0.188

BMI — body mass index

Anaesthesia was then continued in both groups according to the guidelines of the European Society concerning Perioperative Care of the Obese Patient. Anaesthesia was maintained with a mixture of desflurane, air and oxygen. No opioids were administered in the DEX group during the procedure.

Haemodynamic parameters, including systolic and diastolic blood pressure (SBP and DBP, respectively), mean arterial pressure (MAP) and heart rate (HR) were monitored and registered at patient arrival to the operation theatre (T0), after the administration of intravenous premedication (T1), when hypnotic anaesthesia was obtained (BIS < 60, T2) and after tracheal intubation (T3). The difference between pre- and post-intubation values was calculated for each mentioned parameter. An increase of SBP and/or HR by > 20% was considered as sign of inadequate analgesia during tracheal intubation.

Patients in whom the first attempt of tracheal intubation had failed were excluded from final analysis, which incorporated recorded values from 33 persons.

Statistical analyses were performer using the Statistica 11 software (StatSoft, Tulsa, USA). Normal distribution of values was verified using *W* Shapiro Wilk's test. For further comparisons, Student's *t*-test was employed. A *P*-value < 0.05 was deemed the threshold for statistical significance.

RESULTS

No statistically significant differences were found between the groups as to their demographic characteristics (Table 1). In the DEX group, a mean dose of 211 mg propofol (2 SD = 172) was administered in order to reach the desired BIS value, whereas in the FNT group, 194 mg propofol (2 SD = = 103) and 0.21 mg fentanyl (2 SD = 0.2) were given. The values of haemodynamic parameters at respective time points are presented in Table 2.

There were no important differences in mean values of respective parameter changes, recorded before and after intubation. The evolution of the analysed parameters is presented in Figures 1–4.

Table 2. Haemodynamic parameter profiles at respective time points: T0 — baseline, T1 — after premedication with fentanyl and midazolam (FNT group) or fentanyl and dexmedetomidine (DEX group), T2 — after induction of anaesthesia, T3 — after intubation (mean ± SD)

Time point	T0		T1		T2		T3	
Patient group	**DEX**	**FNT**	**DEX**	**FNT**	**DEX**	**FNT**	**DEX**	**FNT**
SPB (mm Hg)	153.7 ± 29.9	152.8 ± 12.8	141.1 ± 20.9	149.3 ± 11.7	125.9 ± 18.7	135.4 ± 15.2	127.2 ± 27.5	146.6 ± 29.9
DBP (mm Hg)	84.7 ± 16.6	85.7 ± 5.5	77.8 ± 7.1	85.4 ± 11.0	68.6 ± 12.8	79.5 ± 13.9	71.3 ± 13.0	83.1 ± 17.1
MAP (mm Hg)	107.11 ± 20.4	109.7 ± 4.6	99.4 ± 11.5	106.5 ± 9.5	89.0 ± 13.9	95.2 ± 12.5	93.1 ± 15.3	103.7 ± 20.4
HR (1 min^{-1})	84.56 ± 13.3	76.0 ± 13.1	84.8 ± 18.9	82.7 ± 11.4	77.7 ± 13.8	81.2 ± 11.5	75.4 ± 11.9	83.8 ± 11.5

Abbreviations are explained in the text

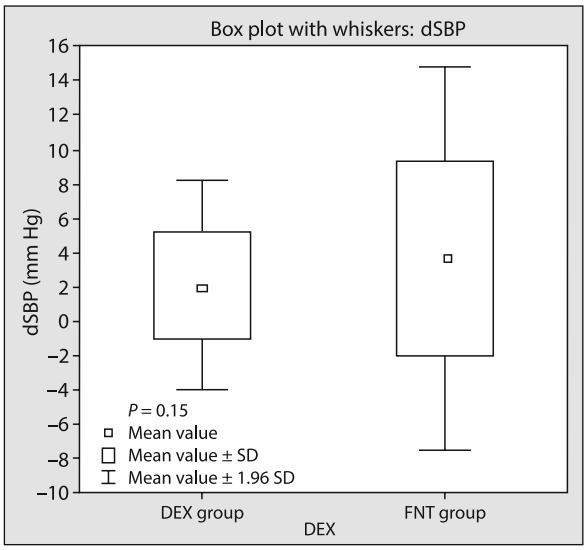

Figure 1. Evolution of SBP value (dSBP) during tracheal intubation

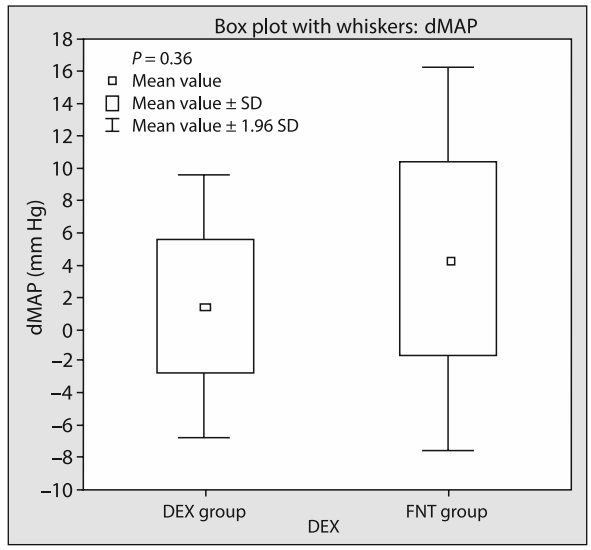

Figure 3. Evolution of MAP value (dMAP) during tracheal intubation

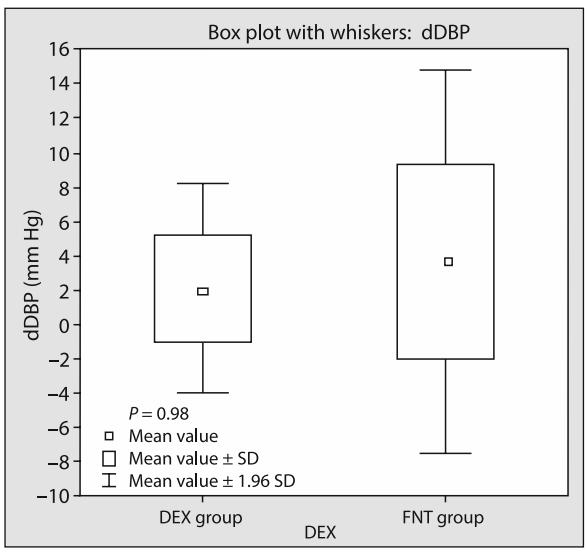

Figure 2. Evolution of DBP value (dDBP) during tracheal intubation

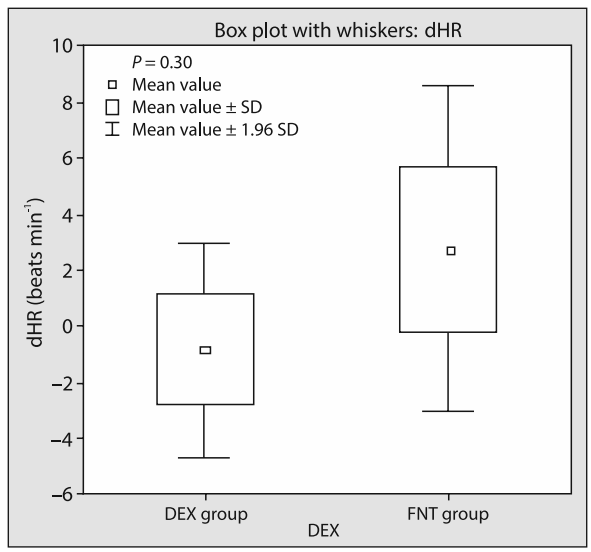

Figure 4. Evolution of HR value (dHR) during tracheal intubation

Mean values of haemodynamic parameters did not increase by 20% from the baseline after intubation. Analyses of individual cases revealed though an increase of at least 20% in three subjects in the FNT group, and in only one patient in the DEX group.

Although no significant differences were found between the groups, the DEX group demonstrated lesser degree of parameter variation, i.e. lower minimal and maximal values registered before and after intubation. This observation suggests greater haemodynamic stability in the DEX group on exposure to a pain stimulus experienced during tracheal intubation.

No patient had a BIS value of over 60 post-intubation.

DISCUSSION

Although adequate anaesthesia relieves the patient of pain, their body experiences a cascade of neuroendocrine reactions [7], mostly related to sympathetic activation of the autonomous nervous system [8]. Opioid administration exerts analgetic function through complex interactions with their receptors, which dampen sympathetic response to pain, in the setting of pharmacologically reduced consciousness [9]. Underlying mechanisms are not well understood but most likely involve the hypothalamus, where fentanyl blocks the release of transmitters affecting stress reaction to surgical intervention [10]. This beneficial effect is, however, accompanied by some adverse reactions. A well-known one is the correlation between intraoperative administration of high opioid doses and post-operative nausea or vomiting, as well as delayed return of peristaltics. Administration of opioids during surgical procedures is also related to post/operative hyperalgesia [11].

Agents affecting the autonomous system selectively should therefore effectively eliminate body reaction to pain stimuli in an anaesthetised patient i.e. who does not feel pain. Following this theory, a couple of years ago the concept of general anaesthesia based on other, non-opioid agents, was introduced. Those were to be equally efficient in pain elimination but to interact with other receptors. Shortly after, agents affecting the sympathetic system, e.g. beta-blockers, were found to inhibit neuroendocrine response to pain stimuli [12]. Other agents that modulate pain response such as lidocaine and ketamine were also found to be useful intraoperatively [6, 13].

The analgetic properties of alpha-2-agonists were first described in 1974, and lack of respiratory depression following use of clonidine was reported shortly afterwards. Dexmedetomidine has eight-fold higher affinity to alpha-2 receptors as compared to clonidine. In USA, dexmedetomidine is registered for sedation in intensive care patients and during surgical interventions. In Poland, the agent is used for sedation in patients hospitalised in intensive care units. Usage of dexmedetomidine was observed to markedly reduce the consumption of analgetics. Since opioids have depressive effect on the respiratory system, patients at risk of developing respiratory complications should be administered other agents, having analgetic properties but devoid of a significant or prolonged influence on respiration.

Dexmedetomidine may thus be used as opioid replacement in general anaesthesia, and may be an equally efficient analgetic during surgical procedures, if administered in adequate doses. The adverse effect profile of this agent is of particular advantage for obese patients who are more prone to CRE, as dexmedetomidine lacks the respiratory depressing effect [14]. Given its mechanism of action that bypasses opioid receptors and thus provides alternative an adverse event profile, dexmedetomidine seems an excellent candidate for a complimentary analgetic in patients at risk. According to the literature, patients anaesthetised with dexmedetomidine had fewer adverse events in the post-operative period [15, 16].

Doses of dexmedetomidine applied for low dose opioid anaesthesia vary greatly in the literature. A loading dose of 0.5 μg kg^{-1} administered intravenously under 10 minutes was proposed, with a maintenance dose of 0.1–0.4 μg kg^{-1} $hour^{-1}$ [17, 18] or in infusion at 0.2–0.8 μg kg^{-1} $hour^{-1}$, initiated at 3-5 minutes prior to the induction of anaesthesia [16]. In the presented study, Polish guidelines for the treatment of post-operative pain were applied. These mention dexmedetomidine as part of multimodal therapy, in a single dose of 200 μg infused slowly before the induction of anaesthesia [6].

Opioid-free or low-opioid-dose anaesthesia may be applied in various patient groups, not only in obese subjects. Indications for this type of anaesthesia include also sleep apnoea syndrome, chronic obstructive pulmonary disease, hypersensitivity to opioids, narcotic abuse or active neoplasia [19]. The usage of dexmedetomidine is contraindicated in cases of circulatory insufficiency, bradyarrhythmia or hypovolaemia [19].

Advantages of dexemedetomidine anaesthesia include avoiding hyperalgesia after surgery, obtaining a stable haemodynamic profile, and a lack of negative effects of opioids, both during and after the operation. The latter include respiratory depression, of particular importance in obese patients [17]. Multimodal analgesia decreases the risk of developing chronic pain [6]. As fewer adverse effects typical for opioids (somnolence, confusion, post-operative nausea and vomiting, constipation) occur in patients receiving dexmedetomidine, their safety and comfort after the procedure becomes markedly improved [18].

Non-opioid or low-dose opioid anaesthesia may be administered using protocols given below.

Clonidine may be infused slowly intravenously at 150 µg before the induction of anaesthesia [6] and/or dexmedetomidine at 200 µg injected slowly intravenously [6] or at 0.5––1.0 µg kg^{-1} IBW infused during 10 minutes [20] and/or 50 mg ketamine as a single intravenous bolus before induction [6] or at 0.125–0.25 mg kg^{-1} [20] and/or lidocaine 1–1.5 mg kg^{-1} IBW in a slow infusion [6, 20].

For low-dose opioid anaesthesia, 100 µg intravenous fentanyl or 10 µg sufentanyl is administered intravenously for premedication [20]. During general anaesthesia, intravenous ketamine at 0.125–0.25 mg kg^{-1} IBW $hour^{-1}$ [4, 20] or lidocaine at 1.5–3 mg kg^{-1} IBW $hour^{-1}$ may be administered [6, 20].

The available literature does not provide any studies describing the use of dexmedetomidine for intraoperative analgesia in obese patients. Tufanogullari *et al.* [16] reported that patients receiving dexmedetomidine had lower MAP values at the moment of skin incision. These authors pointed also to haemodynamic stability in patients operated under dexmedetomidine anaesthesia. Feld *et al.* [17] compared anaesthesia with dexmedetomidine and procedures involving fentanyl. These authors observed that the mean arterial pressure and heart rate were lower in patients given dexmedetomidine for surgical procedures, as compared to fentanyl anaesthesia.

In the presented study, lower values of haemodynamic parameters were also observed in the DEX group, already after premedication, then after induction and following intubation. These observations suggest a lower variability of haemodynamic parameters during induction in patients given dexmedetomidine, as compared to standard fentanyl induction.

To sum up, the presented study demonstrates that dexmedetomidine used for opioid substitution during induction has an equally potent analgetic effect during intubation as compared to full dose fentanyl in obese adult patients.

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