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EDITORIAL

Dexmedetomidine in gastrointestinal endoscopic procedures

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Abstract

Gastrointestinal endoscopy is the gold standard in the examination and the treatment of the diseases of gastrointestinal system, but the disadvantage of being painful process. At this point the sedative and analgesic agents may be important. Dexmedetomidine is a new sedoanalgesic agent which is alternative to benzodiazepines and opioids. It has analgesia, amnesia, sedative and anxiolytic properties. The use of dexmedetomidine as the sole anesthetic agent and as the adjuvant analgesic agent has been published but has not been approved because of the inconsistency of efficacy and safety. The author has been collected the published papers in the literature. This article is aimed to describe the use of dexmedetomidine in various gastrointestinal endoscopic procedures.

Key words: Complication; Safety; Dexmedetomidine; Gastrointestinal endoscopy; Sedation

Core tip: Dexmedetomidine has analgesic, amnesic, sedative and anxiolytic properties. Use of dexmedetomidine as the sole anesthetic agent and as the adjuvant anesthetic agent in various gastrointestinal endoscopic (GIE) procedures has been published. A distinct advantage of dexmedetomidine is the maintenance of respiratory force and preserved airway patency. These properties of dexmedetomidine have verified to be beneficial in high-risk patients. This article is aimed to explain the clinical use of dexmedetomidine for GIE procedures of the published papers in the literature.

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INTRODUCTION

Dexmedetomidine is an alpha-2 adrenergic receptor agonist and has an eight times higher than clonidine for alpha-2 adrenergic receptors. It has sedative, anxiolytic and analgesic properties that produce cardiorespiratory

stability at the therapeutic doses. The use of dexmedetomidine may be expanded as an intravenous drug in the medical procedures[1,2]. Dexmedetomidine is approved by the United States Food and Drug Administration for short-term sedation (< 24 h) in adult patients in the intensive care unit (ICU). It also has been used in combination with other sedoanalgesic drugs during painful procedures. Several reports in the literature have been confirmed about its effective use in various gastrointestinal endoscopic (GIE) procedures, although further controlled studies are needed to reinforce its use. This review is aimed to define the role of dexmedetomidine in GIE procedures.

PHARMACOLOGY OF DEXMEDETOMIDINE

The alpha-2 adrenergic receptors are principally postsynaptic receptors distributed in multiple areas[3]. Sedative and anxiolytic properties are utilized throughout alpha-2 adrenergic receptors in the locus ceruleus of pons. The analgesic effects are employed across the stimulation of alpha-2 adrenergic receptors in the dorsal horn of spinal cord. Dexmedetomidine is an alpha-2 adrenergic receptor and has an eight times higher than clonidine for alpha-2 receptors[4]. Its distribution half-life is 6 min in adults over a dose range of 0.2-0.7 mcg/kg per hour intravenous infusion[5]. Dexmedetomidine is rapidly distributed and has an elimination half-life of 2 h. In addition, dexmedetomidine undergoes biotransformation by cytochrome P-450 and glucoronidation. Its clearance remains unaltered in severe renal impairment. However, the clearance decreased up to 32% in severe hepatic dysfunction. Its metabolites are excreted in urine (95%) and in feces (4%).

Moreover, the activation of postsynaptic alpha-2 receptors leads to sympatholysis and results in hypotension and bradycardia. These effects of dexmedetomidine on arterial blood pressure are biphasic with an initial transient rise with a reflex fall in heart rate. This is accompanied by the reduction of arterial blood pressure and heart rate due to inhibition of central sympathetic outflow and stimulation of presynaptic alpha-2 receptors cause decreased release of noradrenaline leading to further fall in the blood pressure[6]. However, these hemodynamic profiles return to the baseline fifteen minutes later. Dexmedetomidine should be contraindicated in the patients with cardiovascular compromise, severe hypovolemia and atrioventricular nodal block.

Dexmedetomidine does not have any depressant effects on respiratory function even at higher doses with no impairment of ventilation or gas exchange[7]. The ventilatory response to hypercapnia was not affected at a dose that created a negative response to strong stimulation. Dexmedetomidine converges on a natural sleep pathway, activating pathways that promote endogenous non-rapid eye movement sleep to exert its sedative effect[3]. Dexmedetomidine creates a reduction in cerebral metabolic demand of oxygen and cerebral blood flow with a slight reduction in intracranial pressure. Its neuroprotective effect is not well known[8]. It seems to employ analgesic effects at the spinal cord level and at the supraspinal sites[9]. However, the analgesic properties of dexmedetomidine are still controversial.

DEXMEDETOMIDINE IN GASTROINTESTINAL ENDOSCOPY

Generally, propofol alone or in combination with midazolam and/or fentanyl is one of the most widely used regimens for sedation during the GIE procedures[10-12]. However, the combination use of sedatives and/or analgesics with propofol may produce some additional risks. Dexmedetomidine offers a sedation level that facilitates natural sleep and communication and also decreases analgesic requirements. The use of dexmedetomidine for sedation during GIE interventions remains to be established. Importantly, the use of dexmedetomidine for sedation in GIE procedures gives more respiratory safety and hemodynamic stability.

Hasanin and Sira[13] evaluated the sedative, hemodynamic, respiratory and adverse effects of dexmedetomidine and propofol during GIE procedures in the pediatric patients. Eighty pediatric patients with ASA Ⅰ, Ⅱ aged 1-14 years were randomized into dexmedetomidine group or propofol group. Sedation was achieved with propofol 2 mg/kg bolus then infused at a rate of 100 mcg/kg per minute or dexmedetomidine 2.5 mcg/kg over 10 min then infused at a rate of 2 mcg/kg per hour to attain a Ramsay sedation scale (RSS) P5. The HR, MAP, RR and SpO_2 were continuously monitored and analyzed. Times of induction, procedure, recovery, and adverse effects were also reported. The HR values were significantly lower in the dexmedetomidine group at induction, after insertion of endoscope, and during the procedure. There were no significant differences in MAP, RR and SpO_2 values at all time points between the two groups. Induction and recovery times were significantly longer in the dexmedetomidine group. No cases in the dexmedetomidine group presented oxygen desaturation *vs* six patients (15%) in the propofol group ($P = 0.026$). This study confirmed that dexmedetomidine sedation in GIE procedures was safe and efficacy as well as also provided cardiorespiratory stability[13].

Vetsa *et al*[14] reported a retrospective study of dexmedetomidine used for GIE procedures in three years. They aimed to evaluate the procedure completion and adverse event rates. A total of 129 procedures with dexmedetomidine were analyzed. Of these, 29% had failed, and 69% had expected difficult sedation or prolonged procedure, and 70% required narcotics during the procedure. Dexmedetomidine was administered intravenously at a bolus of 1 mcg/kg in 5 min and was maintained at the variable rates. Additionally, midazolam

and meperidine or fentanyl was also administered. The result showed the procedure completion rate was 94%. Higher dexmedetomidine maintenance rate was observed in the successfully completed cases. The most common adverse event was hypotension (37%). The interventions for adverse events were required in 86%. All these adverse events were readily managed without significant morbidity. The authors concluded that the use of dexmedetomidine with standard sedative drugs for GIE procedures was related with excellent procedure completion rate in the difficult to sedate procedures. However, the prolonged recovery period and increased adverse events were also observed[14].

However, many anesthetic agents including dexmedetomidine reduce the lower esophageal sphincter pressure (LESP). The reduction of LESP and the gastroesophageal pressure gradient (GEPG) stimulates gastroesophageal reflux and can cause to aspiration pneumonia. Turan and coworkers compared the effects of dexmedetomidine and propofol on LESP and GEPG in the eleven healthy volunteers. The results demonstrated that no significant differences in LESP and GEPG were observed. They concluded that both dexmedetomidine and propofol had comparable effects on LESP and GEPG. Although both sedative drugs caused some decrease in LESP at high concentrations, it did not create gastroesophageal reflux during the sedation[15].

ESOPHAGOGASTRODUODENOSCOPY

Esophagogastroduodenoscopy (EGD) is an endoscopic procedure for diagnosis and treatment of upper gastrointestinal tract problems. Generally, topical pharyngeal anesthesia is safe for the use as premedication for unsedated EGD procedure. Consequently, the unsedated EGD procedure is also well accepted[16]. However, this procedure causes the patient discomfort and anxiety. The sedative drugs are used to relieve these symptoms and improve the endoscopic outcome.

Recently, a randomized, controlled study is conducted to evaluate the effect of dexmedetomidine and propofol on sedation for EGD procedure in outpatient cases. This study confirmed that dexmedetomidine and propofol offered an acceptable level of sedation without serious adverse effects during EGD procedure. The patients in the dexmedetomidine group demonstrated minimal respiratory-related adverse effects. More patients in the propofol group experienced a deeper level of sedation depth at the start of the procedure[17].

Wu *et al*[18] assessed the efficacy and safety of dexmedetomidine and midazolam for conscious sedation in patients with ASA physical status Ⅰ-Ⅱ who underwent elective EGD procedures. The results of the study demonstrated that patients in the dexmedetomidine group had significantly higher oxygen saturation and overall satisfaction than patients in the midazolam group. Additionally, the patients in the midazolam group experienced a significant decrease in the mean arterial blood pressure during sedation compared with the baseline values. However, no clinically significant complications between the two groups were noted. The authors concluded that dexmedetomidine had a good safety property and was an effective sedation drug for EGD procedure[18].

A randomized controlled study compared the efficacy and safety of dexmedetomidine and midazolam in EGD procedure. The result of the study confirmed that dexmedetomidine was suitable for endoscopic procedures of upper gastrointestinal tract. Furthermore, dexmedetomidine offered shorter recovery time and better patient's satisfaction[19]. The study of Hashiguchi *et al*[20] also demonstrated that dexmedetomidine for sedation during EGD procedure was as effective and safe as midazolam.

Recently, Samson *et al*[21] evaluated and compared the sedation efficacy and hemodynamic effects of midazolam and propofol and dexmedetomidine in the patients underwent elective diagnostic EGD procedure. The 90 patients with ASA physical status Ⅰ or Ⅱ were randomized into three groups; Group Ⅰ received midazolam infusion, Group Ⅱ received propofol infusion and Group Ⅲ received dexmedetomidine infusion. The study demonstrated that endoscopist satisfaction and recovery in the dexmedetomidine group was significantly better than in the midazolam and propofol groups. In addition, mean arterial blood pressure in the propofol group was significantly lesser than in the dexmedetomidine and midazolam groups[21].

The safety and efficacy of dexmedetomidine for sedation in EGD procedure is confirmed. A prospective, randomized study investigated and compared the safety and efficacy of dexmedetomidine and midazolam for sedation in EGD procedure. A total of 50 adult patients with ASA physical status classification Ⅰ and Ⅱ were included. A brief questionnaire was performed to accumulate the demographic data, anxiety score, satisfaction and expected discomfort. Mean arterial blood pressure, heart rate, respiratory rate and oxygen saturation during and after the procedure were measured continuously and recorded every minute. Low levels of procedural discomfort and anxiety scores as well as high satisfaction levels were observed in these two groups. However, the endoscopist satisfaction was significant higher in the patients receiving dexmedetomidine. In addition, the adverse event rate in the midazolam group was higher than in the dexmedetomidine group. The study confirmed that dexmedetomidine was better than midazolam in term of retching, rate of adverse events and endoscopist satisfaction for sedation the patients for EGD procedures[22].

Jiang *et al*[23] studied the sedative effect and hemodynamic influence of dexmedetomidine on the patients undergoing EGD procedure. Forty patients were randomly assigned into two groups. In the control group (C), a single dose of 2.5 mg/kg propofol was infused. In the dexmedetomidine group (D), 0.8 mcg/kg of dexmedetomidine was infused slowly (longer than 10 min) before propofol application. The MAP, HR, SpO_2,

OAA/S, and Ramsay sedation score were recorded at four different time points, before infusion (T0), at beginning of operation (T1), when an endoscope entered the stomach (T2), after the operation was finished (T3). The total dosage of propofol, induction time and arousing time were also observed. The results showed the Ramsay sedation scores at T1, T2 and T3 of group D are statistically higher than group C and the T0 group. In addition, group D also showed the low HR and MAP of the three time points, shorter induction times and arousing times as well as less propofol dosage than group C. No patients showed signs of respiratory suppression. They suggested that the use of 0.8 mcg/kg of dexmedetomidine at periprocedural period of the EGD procedure could yield marked sedative effect, had antihypertensive effect and did not suppress respiration[23].

Moreover, dexmedetomidine can use with the combination of other sedoanalgesic drugs. The case series of the combination use of dexmedetomidine and ketamine for EGD procedures were studied in 46 children aged 2-12 years. Dexmedetomidine 1 mcg/kg and ketamine 2 mg/kg were administered over 5 min. The alteration of mean arterial blood pressure, heart rate, and oxygen saturation was not significantly different from the baseline. In addition, no airway interventions were needed. The results of this case series showed that the combination of dexmedetomidine and ketamine not only promised to be clinically effective but also safe for EGD procedure in the pediatric patients[24]. However, the combination dexmedetomidine and ketamine provided longer sedation times and deeper sedation level when compared to the combination etomidate and fentanyl[25] (Table 1).

Generally, propofol has been used in combination with dexmedetomidine to offer sedation/anesthesia. The pharmacodynamic profile of this combination regimen in 24 children aged 3-10 years underwent EGD procedure was investigated[26]. The plasma propofol concentration at which 50% of the patients presented minimal response to stimuli was evaluated. The result demonstrated that propofol in the combination with dexmedetomidine was no significant shift in the propofol concentration-response curve. The authors accomplished that a concurrent infusion of dexmedetomidine in a dose of 1 mcg/kg did not affect the propofol requirement[26].

Sedation in the patients with obstructive sleep apnea (OSA) is very challenge. Dexmedetomidine offers sedation with minimal respiratory depression which is a desirable characteristic in the patients with OSA. An observational study assessed the safety and efficacy of dexmedetomidine/propofol anesthesia for the patients with OSA without endotracheal intubation during EGD procedure[27]. Twenty patients with high probability of OSA undergoing EGD procedure were enrolled in the study. Dexmedetomidine 1 mcg/kg bolus was administered over 10 min followed by propofol boluses. After that, the anesthesia was maintained by using continuous propofol infusion. The result showed transient hypoxemic events occurred in two patients during the EGD procedure. Additionally, transient hypotension was experienced in three patients during the procedure and three patients in the post-anesthesia care unit. After discharge, 16 patients complained of drowsiness, two patients informed dysphoric symptoms and one patient reported of dry mouth. The study concluded that the combination of dexmedetomidine and propofol could offer acceptable anesthesia for EGD procedure in the patients with OSA. This combination method provided a substitute to tracheal intubation in these high risk patients[27].

Atkins *et al*[28] presented a patient with previously undiagnosed extensive tracheomalacia who suffered airway obstruction during an elective EGD under anesthesia. In the second anesthesia, the authors used 1.5 mcg/kg of dexmedetomidine over 15 min then continuous infusion at a rate of 0.7 mcg/kg per hour and an *iv* bolus of 0.5 mg/kg of ketamine followed by infusion at a rate of 1 mcg/kg per minute. The patient was nonresponsive to the endoscope insertion and preserved normal airway tone with no episodes of any respiratory depression. This case demonstrated the potential advantages of the combination use of dexmedetomidine and ketamine for sedation the patients with achalasia underwent EGD procedure[28].

Another case report of a nine-year-old, 45 kg child with Duchenne muscular dystrophy underwent EGD procedure by using dexmedetomidine was presented. The patient had a history of egg allergy, and the potential risk of malignant hyperthermia. The combination use of dexmedetomidine and ketamine was utilized for procedural sedation. In this case, a bolus dose of 1 mcg/kg of dexmedetomidine and a single dose of 1 mg/kg of ketamine was given and was maintained by dexmedetomidine continuous infusion at a rate of 0.5 mcg/kg per hour. This case report established that this combination regimen used for EGD procedure was successfully completed and the patient accepted the procedure[29].

Additionally, intranasal dexmedetomidine can be used for the endoscopic procedure. Han *et al*[30] compared the cardiorespiratory profiles between intranasal and intravenous dexmedetomidine administered 10 min before induction for the EGD procedure. A dose of 1.5-2 mg/kg of propofol was given for induction. The Mean arterial blood pressure, heart rate, respiratory rate, and oxygen saturation were monitored. The authors concluded that intranasal dexmedetomidine was an effective and safe method alternative to intravenous dexmedetomidine for EGD procedure[30].

Cheung *et al*[31] assessed the efficacy of intranasal dexmedetomidine combined with patient-controlled sedation (PCS) for EGD procedure. Intranasal dexmedetomidine 1.5 mcg/kg or intranasal saline was administered 1 h before the procedure. PCS with propofol and alfentanil was given for rescue sedation. The total requirement of PCS propofol and alfentanil

Table 1 The use of dexmedetomidine in a combination technique for gastrointestinal endoscopic procedures

Ref.	Type of endoscopy	No. of patients	DEX group	Non-DEX group	Summary of findings
Wu *et al*[17]	EGD	70	DEX 1 mcg/kg followed by 0.5 mcg/kg per hour infusion *iv*, FEN 1 mcg/kg *iv*	PRO 0.6 mg/kg and on demand bolus 10-20 mg *iv*	DEX showed minimal adverse effects on respiratory function. More patients in PRO created deeper sedation at start
Cheung *et al*[31]	EGD	50	DEX 1.5 mcg/kg *in*, PCS with PRO and Alfentanil	Normal saline *in*, PCS with PRO and Alfentanil	DEX i.n. with PCS PRO and alfentanil presented deeper sedation with significantly fewer use of additional sedative agents during EGD
[1]EL-Shmaa *et al*[25]	EGD	100	DEX 1 mcg/kg followed by 0.5-1 mcg/kg per hour infusion *iv*, KET 1 mg/kg and on demand bolus 0.5 mg/kg *iv*	ETO 0.15 mg/kg followed by 0.01-0.03 mg/kg per minute infusion *iv*, FEN 1 mcg/kg *iv*	ETO/FEN combination provides shorter sedation times and lighter sedation level compared to DEX/KET combination
Wu *et al*[18]	EGD	60	DEX 0.3 mcg/kg followed by 0.2-0.3 mcg/kg per hour infusion *iv*, FEN 1 mcg/kg *iv*	MDZ 0.05 mg/kg *iv*, FEN 1 mcg/kg *iv*	DEX had a good safety profile and was an effective sedation for EGD procedure
[1]Koksal *et al*[32]	EGD	80	DEX 0.5 mcg/kg followed by 0.2 mcg/kg per hour infusion *iv*, KET 1 mg/kg *iv*	REM 0.5 mcg/kg followed by 0.1 mcg/kg per minute infusion *iv*, KET 1 mg/kg *iv*	REM/KET combination provides faster, more sedoanalgesia and rapid recovery compared with DEX/KET combination
Hashiguchi *et al*[20]	EGD	40	Group D: DEX 6 mcg/kg followed by 0.6 mcg/kg per hour infusion *iv*, Butylscopolamine 20 mg *im*, Lidocaine viscous 5 mL gurgling	Group M: MDZ 0.05 mg/kg *iv*, Butylscopolamine 20 mg *im*, Lidocaine viscous 5 mL gurgling; Group L: Lidocaine viscous 5 mL gurgling	DEX is as safe and effective as MDZ. DEX significantly reduces blood pressure and heart rate
Saleh *et al*[56]	Esophageal dilatation	60	Group D: DEX 2 mcg/kg followed by 0.4 mcg/kg per hour infusion *iv*, MDZ 0.05 mg/kg *iv*	Group P: PRO 1 mg/kg followed by 5 mg/kg per hour infusion *iv*; Group K: KET 2 mg/kg and on demand 0.5 mg/kg *iv*, Atropine 0.02 mg *iv*	DEX-MDZ combination and KET had more stable cardiorespiratory profiles, with adequate postprocedural analgesia
Ayazoglu *et al*[37]	Colonoscopy	121	DEX 0.2 mcg/kg *iv*, PRO 0.5-3 mg/kg per hour infusion *iv*	Group 1: SUF 0.1 mcg/kg in, PRO 0.5-3 mg/kg per hour infusion *iv*; Group 2: MEP 0.4 mg/kg *iv*, PRO 1 mg/kg bolus followed by 0.5-3 mg/kg per hour infusion *iv*; Group 3: MEP 0.4 mg/kg *iv*, MDZ 0.03 mg/kg *iv*, PRO 0.5-3 mg/kg per hour infusion *iv*	Sedation for colonoscopy can be safely and effectively utilized with low doses of PRO combined with DEX, in SUF, *iv* MEP and *iv* MEP with MDZ
Techanivate *et al*[36]	Colonoscopy	70	DEX 1 mcg/kg *iv*, FEN 0.5 mcg/kg *iv*, PRO 20 mg and on demand 20 mg *iv*	FEN 0.5 mcg/kg *iv*, PRO 1 mg/kg and on demand 20 mg *iv*	DEX for sedation in colonoscopy reduced hypotension incidence than PRO
Dere *et al*[34]	Colonoscopy	60	DEX 1 mcg/kg followed by 0.5 mcg/kg per hour infusion *iv*, FEN 1 mcg/kg *iv*	MDZ 0.05 mg/kg *iv*, FEN 1 mcg/kg *iv*	DEX provided more hemodynamic stability, higher sedation scores, higher satisfaction scores and lower pain scores
Abdalla *et al*[43]	ERCP	60	DEX 1 mcg/kg followed by 0.5 mcg/kg per hour infusion *iv*, PRO 5 mg/kg per hour and on demand bolus 0.5 mg/kg *iv*	KET 1 mg/kg followed by 0.5 mg/kg per hour infusion *iv*, PRO 5 mg/kg per hour and on demand bolus 0.5 mg/kg *iv*	DEX-PRO during ERCP showed better hemodynamic stability, less nausea/vomiting and shorter recovery time when compared with KET-PRO combination
[1]Ramkiran *et al*[54]	ERCP	72	DEX 1 mcg/kg followed by 0.5 mcg/kg per hour infusion *iv*, MDZ 0.05 mg/kg *iv*, Hyoscine 0.3 mg/kg *iv*, PRO 0.5-1.5 mg/kg and on demand bolus 20 mg *iv*	Group K: KET 0.25 mg/kg followed by 5 mcg/kg per minute infusion *iv*, MDZ 0.05 mg/kg *iv*, Hyoscine 0.3 mg/kg *iv*, PRO 0.5-1.5 mg/kg and on demand bolus 20 mg *iv*; Group C: normal saline *iv*, MDZ 0.05 mg/kg *iv*, Hyoscine 0.3 mg/kg *iv*, PRO 0.5-1.5 mg/kg and on demand bolus 20 mg *iv*	Low dose KET with PRO boluses resulted in lesser PRO consumption, with earlier recovery and favorable hemodynamics compared with DEX in outpatient ERCP
Mukhopadhyay *et al*[46]	ERCP	45	DEX 1 mcg/kg followed by 0.5 mcg/kg per hour infusion *iv*, MDZ 0.5 mg/kg *iv*, Pentazocine 6 mg *iv*, KET 25 mg *iv*, PRO 0.75-1 mg/kg and on demand bolus 10-20 mg *iv*	Group 1: MDZ 1 mg/kg *iv*, PRO 0.75-1 mg/kg and on demand bolus 10-20 mg *iv*; Group 2: MDZ 0.5 mg/kg *iv*, Pentazocine 6 mg *iv*, KET 25 mg *iv*, PRO 0.75-1 mg/kg and on demand bolus 10-20 mg *iv*	DEX increased efficacy and safety of sedate-analgesic cocktail. It reduces PRO requirement, more stable level of sedation and increases anesthetist satisfaction

Sethi *et al*[42]	ERCP	60	DEX 1 mcg/kg followed by 0.5 mcg/kg per hour infusion *iv*, FEN 1 mcg/kg *iv*	MDZ 0.04 mg/kg and on demand bolus 0.5 mg *iv*, FEN 1 mcg/kg *iv*	DEX could be a superior alternative drug to MDZ for conscious sedation in ERCP
[1]Mazanikov *et al*[53]	ERCP	50	DEX 1 mcg/kg followed by 0.7 mcg/kg per hour infusion *iv*, PCS with PRO and Alfentanil	Group P: Normal saline, PCS with PRO and Alfentanil	DEX alone was insufficient in alcoholics. PCS with PRO and Alfentanil could be recommended
[1]Nagaraj *et al*[51]	ERCP	70	DEX 1 mcg/kg followed by 0.5 mcg/kg per hour infusion *iv*, FEN 1 mcg/kg *iv*	PRO 0.5 mg/kg followed by 2 mg/kg per hour infusion *iv*, FEN 1 mcg/kg *iv*	PRO/FEN combination provided better overall conditions when compared to DEX/FEN combination

[1]Negative result of dexmedetomidine. EGD: Esophagogastroduodenoscopy; ERCP: Endoscopic retrograde cholangiopancreatography; DEX: Dexmedetomidine; MDZ: Midazolam; PRO: Propofol; FEN: Fentanyl; MEP; Meperidine; REM: Remifentanil; ETO: Etomidate; KET: Ketamine; SUF: Sufentanil; PCS: Patient controlled sedation.

in the dexmedetomidine group was significantly lesser than in the saline group. There were no significant differences in recovery phase, adverse events and satisfaction between the two groups. The authors concluded that intranasal dexmedetomidine with propofol and alfentanil for PCS presented deeper sedation with significantly fewer use of supplementary sedative agents during the EGD procedure[31].

Recently, Koksal *et al*[32] compared the effects of adding dexmedetomidine to ketamine on the safety and efficacy of anesthesia for EGD procedures. They used a loading dose of 0.5 mcg/kg of dexmedetomidine, followed by a continuous infusion of 0.2 mcg/kg per minute and a bolus dose of 1 mg/kg of ketamine compared with a loading dose of 0.5 mcg/kg of remifentanil, followed by a continuous infusion of 0.1 mcg/kg per minute and a bolus dose of 1 mg/kg of ketamine. Additionally, a bolus dose of 0.5-1 mg/kg of propofol was supplemented if inadequate sedation occurred. The authors concluded that a combination use of dexmedetomidine and ketamine offered lesser efficacy and relatively longer recovery phase than the combination of remifentanil and ketamine[32]. This negative result of a combination of dexmedetomidine and ketamine could be due to relatively small dose of dexmedetomidine (Table 1).

COLONOSCOPY

Colonoscopy is the gold standard in the examination and the treatment of the disease of lower gastrointestinal tract. The ideal sedative agent for this procedure should permit a rapid adjustment of the sedation level and should not have any side effects[33]. Currently, several studies of the use of dexmedetomidine for colonoscopy are published. A previous study compared the effects of dexmedetomidine and midazolam on hemodynamic parameters, efficacy of sedation, satisfaction and recovery scores during colonoscopy. This study confirmed that dexmedetomidine offered more hemodynamic stability, lower pain scores as well as higher sedation and satisfaction scores in colonoscopic procedure[34].

Sula *et al*[35] evaluated the efficacy and side effects of dexmedetomidine and propofol. They prospectively studied 231 patients with ASA class Ⅰ-Ⅲ underwent colonoscopy. Sedation was accomplished with propofol 1.5 mg/kg and on demand bolus dose of 0.4-0.5 mg/kg (group P) and with dexmedetomidine 1 mcg/kg (group D). Arterial blood pressure, heart rate, respiratory rate, oxygen saturation values as well as the patients' satisfaction and the endoscopists' satisfaction were compared. A decline in the systolic blood pressure occurred in 29 patients (12.5%), 17 patients (58.6%) in the group D and 12 patients (41.4%) in group P. Eleven patients (4.7%) in group P and one patient in group D had a decline in oxygen saturation. All these adverse effects were not clinically significant, and without serious effects. No severe bradycardia was noted. The satisfaction scores in both groups were comparable. The authors suggested that both regimens were safe and effective for sedation during colonoscopic procedure. The use of propofol initiated more desaturation, while the use of dexmedetomidine caused more hypotension[35].

Another study of the hemodynamic parameters of dexmedetomidine for sedation in colonoscopy was presented. Seventy patients with ASA physical status Ⅰ-Ⅲ were randomized into two groups. In group P, the patients were received 0.5 mcg/kg of fentanyl over 5 min, and maintained by 1 mg/kg of propofol. In group D, the patients were received 1 mcg/kg of dexmedetomidine with 0.5 mcg/kg of fentanyl over 5 min, followed by 20 mg of propofol. The 20 mg propofol was titrated as required to achieve the target bispectral index (BIS) and sedation score. The results showed that the incidence of hypotension in group P was significantly higher than in group D. Heart rate in group P was greater than group D at 10th minute and from 25th minute throughout the period of colonoscopy. There were no significant differences in the induction time, incidence of bradycardia, patient satisfaction and postprocedural complications between the two groups. Additionally, the patients in group D recovered from sedation more quickly than in group P[36].

Several sedation regimens are administered during colonoscopy. To date, the propofol-based sedation regimens are commonly used. The safety, efficacy and patient satisfaction of propofol combined with dexmedetomidine for conscious sedation in the colonoscopy were evaluated by Ayazoğlu *et al*[37]. The patients in the dexmedetomidine combination with propofol group accomplished a greater degree of sedation and a rapid

recovery activity when compared with the meperidine, sufentanil and midazolam in combination with propofol groups. The authors recommended that sedation for colonoscopy could be effectively and safely done with propofol combined with dexmedetomidine and other sedoanalgesic drugs[37].

However, the sole use of dexmedetomidine has inadequate utility for sedation during outpatient colonoscopy. For example, the study of Jalowiecki *et al*[38] showed that dexmedetomidine sedation for colonoscopic procedure was incomplete because of its adverse effects including prolonged recovery and hemodynamic instability. The authors evaluated the capability of dexmedetomidine sedation for 64 patients underwent outpatient colonoscopic procedures. In group D, patients received 1 mcg/kg of dexmedetomidine over 15 min and maintained by an infusion of 0.2 mcg/kg per hour. Group P received 1 mg/kg of meperidine and 0.05 mg/kg of midazolam. Group F, patients received 0.1-0.2 mg of fentanyl *iv* on demand. The study was terminated because of adverse effects in group D. There was a significantly greater reduction in heart rate and arterial blood pressure in group D. In group D, additional fentanyl was needed in 47% of patients compared with 42.8% and 79.2% of patients in group P and F, respectively. Nausea/vomiting, vertigo and ventricular arrhythmia were noted only in group D. In addition, group D had the longest time to home readiness[38]. This limited utility of dexmedetomidine for sedation during outpatient colonoscopy might be due to a relatively low dose during the procedure and inadequate analgesia (Table 2).

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

Endoscopic retrograde cholangiopancreatography (ERCP) is a routinely carried out diagnostic and/or therapeutic procedure of many pancreatic and biliary diseases. It is a distressing procedure in awaked patients. These patients require sedation/anesthesia mainly to minimize their anxiety and analgesics to lessen pain and discomfort thereby enhancing patient's cooperation throughout the procedure[39].

Kilic *et al*[40] presented the use of dexmedetomidine for sedation during ERCP procedure. The efficacy, hemodynamic parameters and adverse effects were compared between dexmedetomidine and midazolam[40]. Fifty patients aged 18-80 years were randomized into two groups. Group M, patients received a bolus infusion of 0.04 mg/kg of midazolam, and followed by a supplementary dose of 0.5 mg midazolam. Group D, patients received a bolus infusion of 1 mcg/kg per hour of dexmedetomidine over 10 min, and maintained by a continuous infusion of 0.2-0.7 mcg/kg per hour. All patients were sedated to target a Ramsay scale of 3-4. Heart rate in group D was significantly lesser than group M. In addition, the dexmedetomidine group also showed higher endoscopist satisfaction scores[40].

Furthermore, Ceylan *et al*[41] evaluated the effects of propofol and dexmedetomidine hemodynamics, adverse effects, cognitive functions, and satisfaction during ERCP procedure. The fifty patients with ASA physical status class Ⅰ and Ⅱ were randomized into the two groups. Group P received propofol 75 mcg/kg per hour *iv* over 10 min, and followed by an infusion of 12.5-100.0 mcg/kg per minute. Group D received dexmedetomidine 1 mcg/kg per hour over 10 min, and maintained by an infusion of 0.2-0.7 mcg/kg per hour. All patients were sedated to attain a RSS of 3-4. The mental status examination before and after the procedure as well as pain was evaluated. The blood pressure and heart rate values in group D were significantly lesser than in group P. However, there were no significant differences in patient and endoscopist satisfaction among the two groups[41].

Dexmedetomidine has been tried for various endoscopic procedures, and the evidence occurs to recommend its use for ERCP procedure. A randomized controlled study was planned to evaluate the hemodynamic and the recovery profiles of dexmedetomidine and midazolam. It was also to assess the grade of comfort and the procedural performance. All patients received 1 mcg/kg of fentanyl at the start of ERCP. Group M received a bolus dose of 0.04 mg/kg of midazolam and supplementary 0.5 mg doses. Group D received a bolus dose of 1 mcg/kg of dexmedetomidine at over 10 min and maintained by a continuous infusion of 0.5 mcg/kg per hour. The targeted depth of sedation was a RSS score 3-4. The heart rate, blood pressure, respiratory rate, oxygen saturation, the time to accomplish the targeted depth of sedation and pain score were evaluated and compared during and after the ERCP procedure. Heart rate and pain scores in group D were significantly lower than in group M. There were no significant differences in mean blood pressure and respiratory rate. The modified Aldrete score of 9-10 at 5 min during recovery was achieved in 27 (90%) patients in group D in contrast to 5 (17%) patients in group M ($P < 0.05$). Dexmedetomidine also showed higher patient and endoscopist satisfaction scores ($P < 0.05$)[42].

The efficacy of dexmedetomidine for anesthesia in ERCP procedure was evaluated by Abdalla *et al*[43]. Sixty patients with ASA physical status class Ⅱ or Ⅲ underwent ERCP procedures were randomly assigned into two groups. Group D, patients received a bolus dose of dexmedetomidine 1 mcg/kg and maintained by 0.5 mcg/kg per hour. Group K, patients received a loading dose of ketamine 1 mg/kg and followed by 0.5 mg/kg per hour. Propofol was used for induction of anesthesia and atracurium was utilized for endotracheal intubation. After that, anesthesia was maintained by continuous infusion of propofol. The combination of dexmedetomidine and propofol during ERCP procedure showed better hemodynamic stability, less nausea and vomiting, as well as shorter recovery time when compared with the combination of ketamine and

Table 2 The use of dexmedetomidine in a single agent technique for gastrointestinal endoscopic procedures

Ref.	Type of endoscopy	No. of patients	DEX group	Non-DEX group	Summary of findings
Samson *et al*[21]	EGD	90	DEX 1 mcg/kg followed by 0.5 mcg/kg per hour infusion *iv*	MDZ 0.04 mg/kg followed by an additional dose of 0.5 mg *iv*	Endoscopist satisfaction and recovery in DEX group was significantly better than in MDZ and PRO groups
Jiang *et al*[23]	EGD	40	DEX 0.8 mcg/kg *iv*	PRO 2.5 mg/kg *iv*	DEX could yield marked sedative effect, had antihypertensive effect and did not suppress respiration
Demiraran *et al*[22]	EGD	50	DEX 1 mcg/kg followed by 0.2 mcg/kg per hour infusion *iv*	MDZ 0.07 mg/kg (total dose 5 mg) *iv*	DEX was superior to MDZ with regard to retching, rate of adverse events and endoscopist satisfaction for EGD sedation
Sula *et al*[35]	Colonoscopy	231	DEX 1 mcg/kg *iv*	PRO 1.5 mg/kg and on demand bolus 0.4-0.5 mg/kg *iv*	Both regimens were effective and safe for sedation. PRO caused more desaturation, while DEX caused more hypotension
[1]Jalowiecki *et al*[38]	Colonoscopy	64	Group D: DEX 1 mcg/kg followed by 0.2 mcg/kg per hour infusion *iv*	Group P: 1 mg/kg of MEP with 0.05 mg/kg of MDZ *iv*, Group F: 0.1-0.2 mg of FEN *iv* on demand	There was a significantly greater decrease in heart rate and blood pressure in group D. Time to home readiness was the longest in group D
[1]Eldesuky Ali Hassan *et al*[48]	ERCP	50	Group D: DEX 1 mcg/kg followed by 0.5 mcg/kg per hour infusion *iv*	Group K: ketofol 1 mg/kg *iv* bolus followed by 50 mcg/kg per minute infusion *iv*	Time to achieve sedation score and total dose of rescue sedation were not significantly different. Patient and endoscopist satisfaction in group K was significantly higher than in group D
Kilic *et al*[40]	ERCP	50	Group D: DEX 1 mcg/kg followed by 0.2-0.7 mcg/kg per hour infusion *iv*	Group M: MDZ 0.04 mg/kg followed by an additional dose of 0.5 mg *iv*	DEX showed higher endoscopist satisfaction. Coughing, nausea and vomiting were observed in three patients in group M, but no patients in group D
Ceylan *et al*[41]	ERCP	50	Group D: DEX 1 mcg/kg followed by 0.2-0.7 mcg/kg per hour infusion *iv*	Group P: PRO 75 mcg/kg per hour followed by 12.5-100.0 mcg/kg per minute infusion *iv*	Blood pressure and heart rate values in group D were significantly lower than in group P. There were no significant differences in patient and endoscopist satisfaction
[1]Muller *et al*[52]	ERCP	26	Group D: DEX 1 mcg/kg followed by 0.2-0.5 mcg/kg per hour infusion *iv*	Group P: PRO (target plasma concentration 2-4 mcg/mL) with FEN 1 mcg/kg *iv*	DEX alone was not as effective as PRO combined with FEN. DEX was associated with greater hemodynamic instability and a prolonged recovery period
Eberl *et al*[55]	Esophageal intervention	64	DEX 1 mcg/kg (0.5 mcg/kg in age > 65) followed by 0.7-1 mcg/kg per hour infusion *iv*	PRO Target Controlled Infusion (OAAS scale ≤ 4)	DEX was a new representative for endoscopic sedation. The acceptance level after PRO was relatively high compared with DEX
Takimoto *et al*[58]	ESD	90	Group D: DEX 3 mcg/kg followed by 0.4 mcg/kg per hour infusion *iv*	Group P: PRO 5 mg bolus and 3 mg/kg per hour infusion *iv*, Group M: MDZ 0.1 mg/kg *iv*	DEX was effective and safe for patients with gastric tumors who underwent ESD

[1]Negative result of dexmedetomidine. EGD: Esophagogastroduodenoscopy; ERCP: Endoscopic retrograde cholangiopancreatography; DEX: Dexmedetomidine; MDZ: Midazolam; PRO: Propofol; FEN: Fentanyl; MEP: Meperidine; REM: Remifentanil; ETO: Etomidate; KET: Ketamine; SUF: Sufentanil; PCS: Patient controlled sedation.

propofol[43].

Moreover, Han-wei *et al*[44] observed the safety and feasibility of dexmedetomidine and fentanyl for conscious sedation in the ERCP procedure. Sixty patients of ASA class Ⅰ-Ⅱ who planned to receive ERCP were allocated into dexmedetomidine group and propofol group. The patients in the two groups were treated with anisodamine 10.0 mg and fentanyl 1.0 mcg/kg before ERCP. The patients in dexmedetomidine group were treated with dexmedetomidine 0.5 mcg/kg by injection within 15 min, then the dexmedetomidine was infused continuously at the rate of 0.5-1.0 mcg/kg per hour to the end of operation. Patients in the propofol group were treated with propofol 1.0 mg/kg in 2 min, and followed by continuous infusion of 4.0-6.0 mg/kg per hour to the end of operation. Arterial blood pressure, heart rate and oxygen saturation were noted at the time points of before anesthesia (T0), before inserting endoscope (T1), while inserting endoscope (T2), 20 min after inserting endoscope (T3) and 10 min after the

end of examination (T4). The intubation process and cooperation of patients were scored; and the patients' satisfaction for examination was evaluated next day. In dexmedetomidine group, heart rate of patients at the time points of T1, T2, T3 and T4 was significantly lower than that at the time point of T0; but there was no significant difference in the systolic and diastolic blood pressure among the time points of T0, T1, T2, T3 and T4. There was no significant difference in the oxygen saturation all time points in the two groups. The heart rate at the time points of T1, T2, T3 and T4 in the propofol group was significantly higher than that in the dexmedetomidine group. The score of intubation process and cooperation of patients in the dexmedetomidine group was significantly higher than that in the propofol group. However, patient satisfaction in both groups was not significantly different. The authors concluded that dexmedetomidine and fentanyl for conscious sedation in ERCP procedure was safe and feasible, which could meet the test needed of sedation, and could obtain better cooperation of the patients[44].

Generally, the combination regimens are commonly used for invasive procedures. Dexmedetomidine may employ a synergistic effect in the combination with sedoanalgesic drugs. Lee and coworkers evaluated the efficacy and adverse effects of midazolam-meperidine-dexmedetomidine (MMD) and midazolam-meperidine (MM) for ERCP procedure in 110 patients. Lower additional and total doses of midazolam were needed in group MMD. Oxygen desaturation and pain scores in group MMD were significantly lesser than in group MM. In addition, the satisfaction scores in group MMD were significantly greater than group MM. The authors recommended that the combination of dexmedetomidine, midazolam and meperidine regimen presented superior sedative efficacy and a greater safety profile during ERCP procedure compared with the combination of midazolam and meperidine regimen[45]. Recently, Mukhopadhyay *et al*[46] assess the safety and efficacy of dexmedetomidine as an add-on for deep sedation in prolonged ERCP procedure. The authors concluded that the addition of dexmedetomidine in sedoanalgesic cocktail increased the safety and efficacy of deep sedation[46].

Ketofol, a combination of ketamine and propofol, is significant interest as an agent for procedural sedation. This combination regimen has several advantages in the terms of hemodynamic stability, lack of respiratory depression, post-operative analgesia and recovery[47]. Recently, a double-blind randomized study is carried out to evaluate two techniques of moderate sedation for patients undergoing ERCP procedure, using either dexmedetomidine or ketofol as regards hemodynamic, sedation, respiratory effect, pain, recovery time, patient and endoscopist satisfaction as well as the complications. Fifty patients were randomly assigned in the two groups; dexmedetomidine received 1 mcg/kg *iv* bolus over 10 min followed by 0.5 mcg/kg per hour or ketofol received 1 mg/kg *iv* bolus and maintained by 50 mcg/kg per minute. Mean arterial pressure and heart rate in the dexmedetomidine group were significantly lesser than in the ketofol group. Additionally, time to achieve RSS score and total dose of rescue sedation in both groups were not significantly different. However, patient and endoscopist satisfaction in the ketofol group was significantly higher than in the dexmedetomidine group[48] (Table 2). The advantage of ketofol in this study may be due to design of the study. The depth of sedation level was targeted to attain a RSS score of 4. The combination use of ketamine and propofol offered better outcome variables than the use of dexmedetomidine alone.

Several case studies also have been reported the efficacy of dexmedetomidine for procedural sedation in the difficult patients. For example, Srivastava *et al*[49] reported a 65-year-old female presented with anorexia, vomiting and yellowish discoloration of skin for 3 mo. The patient was diagnosed as extrahepatic cholangiocarcinoma with extrahepatic biliary obstruction type 3 and was advised surgical resection of tumor. The patient had history of dyspnea on mild exertion (New York Heart Association Ⅲ), left bundle branch block, and cardiomegaly. The transthoracic echocardiography demonstrated dilated left ventricle, global hypokinesia, ejection fraction 25%, moderate pulmonary artery hypertension. However, the patient refused for surgery owing to increased cardiac risk. The patient was advised endoscopic placement of stents to drain the biliary system for symptomatic relief. Monitored anesthesia care with light sedation was required for this procedure. She was induced with 1 mcg/kg of dexmedetomidine over 20 min and then continuous infusion was titrated between 0.2 and 0.5 mcg/kg per hour to keep blood pressure and HR within 10% of baseline. Mean HR during procedure was 74 ± 10 beats/min, and mean blood pressure was 80 ± 15 mmHg. The total procedure time was 40 min. The patient was oxygenated throughout the procedure until recovery from sedation by face mask. The SpO_2 was never below 98%. The recovery time was 30 min[49].

Ko *et al*[50] presented a 10-year-old boy, 29 kg with obstructive jaundice and a distal common bile duct stone. Five days before, ERCP sedation performed by a gastroenterologist was failed. Non-invasive blood pressure, electrocardiography, SpO_2, BIS values and Observer's Assessment of Alertness/Sedation scores were monitored. In this second sedation, a dose of 0.5 mg/kg of ketamine and 0.5 mcg/kg of fentanyl were given before the procedure. Additionally, a bolus dose of 0.7 mcg/kg of dexmedetomidine was given over 10 min followed by a continuous infusion of 0.5 mcg/kg per hour. The oxygen saturation decreased to 85% for a second. However, oxygen saturation recovered to 100% when the scope was inserted. Oxygen supplementation was administered and a child breathed spontaneously. This procedure was successfully completed with minimal decreases in blood pressure and heart rate. After the procedure, dexmedetomidine infusion was stopped.

The patient did not report of postprocedural nausea and vomiting and did not present emergence agitation or delirium[50].

However, the negative results of the use of dexmedetomidine for ERCP procedure have been occurred (Table 2). For example, the study of Nagaraj *et al*[51] compared the combination of dexmedetomidine and fentanyl with the combination of propofol and fentanyl for procedural sedation in ERCP procedure. In the dexmedetomidine group, patients received fentanyl 1 mcg/kg and a bolus dose of dexmedetomidine 1 mcg/kg over 10 min followed by a maintenance dose of 0.5 mcg/kg per hour intravenously. In the propofol group, the patients received fentanyl 1 mcg/kg and a loading dose of propofol infused at 0.5 mg/kg over 10 min followed by a maintenance dose of 2 mg/kg per hour intravenously. The study showed that the combination of propofol and fentanyl achieved better overall conditions for ERCP compared to the combination of dexmedetomidine and fentanyl[51].

Generally, deep sedation is utilized for invasive GIE procedures including ERCP. A combination of two or more sedative drugs produces a synergistic effect and is commonly used for deep sedation technique. Another negative result of the use of dexmedetomidine alone was published by Muller *et al*[52]. They conducted a randomized, double blind, study to test the hypothesis that dexmedetomidine was as effective as propofol combined with fentanyl for sedation during an ERCP procedure. Twenty-six patients with ASA physical status class Ⅰ to Ⅲ were randomly assigned to receive either propofol combined with fentanyl 1 mcg/kg, or dexmedetomidine 1 mcg/kg in 10 min, followed by 0.2 to 0.5 mcg/kg per minute. Supplementary sedative drugs were added if an inadequate sedation was not attained. Heart rate, blood pressure, respiratory rate and oxygen saturation were continuously monitored. The result of the study proved that dexmedetomidine alone was not as effective as a combination of propofol and fentanyl for sedation during ERCP procedure. Moreover, dexmedetomidine was related with lesser hemodynamic stability and prolonged recovery period[52].

Similarly, the use of dexmedetomidine alone for sedation in the alcoholic patients is also inadequate (Table 1). This outcome was confirmed by the study of Mazanikov *et al*[53]. They assessed the suitability of dexmedetomidine for sedation of the alcoholic patients during ERCP procedure. Fifty patients with chronic alcoholism underwent elective ERCP procedure were randomly assigned to receive dexmedetomidine (group D) (a bolus dose of 1 mcg/kg in 10 min, followed by continuous intravenous infusion 0.7 mcg/kg per hour) or normal saline (group P). Additionally, PCS with propofol and alfentanil was used by patients as a rescue method. Sedation was considered as successful if no intervention of an anesthesiologist was needed. Consumption of sedatives was registered, and sedation levels and vital signs were monitored. The result of the study indicated that the use of dexmedetomidine alone was insufficient in all alcoholic patients. The mean consumption of propofol was 159 ± 72 mg in group P, and 116 ± 61 mg in group D (P = 0.028). Sedation was successful in 19 of 25 (76%) patients in group D and all patients in group P (P = 0.022). The incidence of sedation-related adverse events in both groups was comparable. However, dexmedetomidine was associated with delayed recovery. They suggested that PCS with propofol and alfentanil but not dexmedetomidine could be recommended for sedation of the alcoholic patients during ERCP procedure[53]. Additionally, a negative result of the use of dexmedetomidine was also reported by Ramkiran *et al*[54]. The report showed that the use of dexmedetomidine presented in greater propofol consumption, with delayed recovery and unfavorable hemodynamic profiles when compared with a combination of low dose ketamine and propofol in outpatient ERCP procedure[54].

ESOPHAGEAL INTERVENTION

Early neoplastic lesions in esophagus could be treated by endoscopic intervention has evolved as a valid. These esophageal interventions are minimal invasive treatment options alternative to the surgical operations. The safety and effectiveness of dexmedetomidine sedation for endoscopic esophageal interventions was observed in the study of Eberl *et al*[55]. The 64 patients were randomly allocated to the propofol and the dexmedetomidine groups. The effectiveness of sedation was the primary outcome of the study. Respiratory and hemodynamic complications were the secondary outcome variables. The authors suggested that dexmedetomidine was a new representative for endoscopic sedation. However, the sedation efficacy in the propofol group was relatively high compared with the dexmedetomidine group[55].

To date, esophageal strictures after accidental ingestion of a corrosive substance are still clinical problems and the esophageal dilatation sessions are frequently required. The use of dexmedetomidine for these esophageal interventions in children is perceived. The combination of dexmedetomidine and the sedoanalgesic agents was used to evaluate the safety, efficacy, recovery profiles and hemodynamic parameters with those of the combination of propofol and ketamine in pediatric patients underwent endoscopic esophageal balloon dilatation[56]. The study verified that the combination of dexmedetomidine, ketamine and midazolam had relatively more hemodynamic and respiratory stabilities, with adequate postprocedural analgesia. However, the use of ketamine alone had quicker onset and rapid recovery of sedation than the combination of dexmedetomidine and midazolam[56].

ENDOSCOPIC SUBMUCOSAL DISSECTION

Endoscopic submucosal dissection (ESD) is an endos-

copic treatment of early gastric cancer. It has been extensively accepted. However, ESD is correlated with a longer procedure time and a higher risk of patient distress than the conventional endoscopic procedures. An acceptable and safe sedation is necessary. A combination of benzodiazepines and analgesics are usually utilized for sedation, but a new sedative agent such as dexmedetomidine is estimated to be a useful agent[57].

Takimoto and coworkers conducted a randomized study of dexmedetomidine sedation in 90 patients with gastric tumors underwent the ESD procedure. All patients were sedated either with dexmedetomidine (a bolus of 3.0 mcg/kg per hour in 5 min followed by a continuous infusion of 0.4 mcg/kg per hour), propofol, or midazolam. The resection of gastric tumor was completed in 88 (98%) patients. No patients in the dexmedetomidine group demonstrated a significant decrease of the oxygen saturation level. This study proved that sedation with dexmedetomidine was safe and effective for patients with gastric tumors who underwent ESD procedure[58].

Ishibashi *et al*[59] assessed the efficacy and safety of sedation with dexmedetomidine in the intubated spontaneously breathing patients after ESD procedure for pharyngeal or esophageal cancer. The 55 patients with ASA class Ⅰ or Ⅱ who underwent ESD under general anesthesia and who were remained intubated until the next day in the ICU receiving sedation with dexmedetomidine. A continuous infusion of dexmedetomidine at 0.4-0.7 mcg/kg per hour was administered during procedure and continued in the ICU until extubation. Hemodynamic and respiratory parameters as well as the Richmond Agitation Sedation Scale (RASS) scores were noted. The 39 patients in group G were remained well sedated (RASS < 1). The 16 patients were poorly sedated (RASS ≥ 1 at any time-point) were in group P. Hemodynamic and respiratory variables in the ICU were not significantly different between the two groups. The requirements of rescue sedatives and analgesics in group P were significantly higher than in group G. The authors concluded that sedation with dexmedetomidine in the intubated spontaneously breathing patients after ESD was safe and effective. The higher plasma concentration of dexmedetomidine at the time of entrance into the ICU was associated with better sedation and less analgesic requirements[59].

The combination of dexmedetomidine and propofol for the ESD procedure is also safe and effective. Forty patients with ASA physical status class Ⅰ or Ⅱ underwent ESD were randomized into two groups. Group A was given propofol alone. Group B was given intravenously dexmedetomidine followed by propofol. The study demonstrated that the use dexmedetomidine combined with propofol and propofol alone were no significant differences in the respiratory rate, oxygen saturation, operative time and anesthetic effect. This study confirmed that anesthetic effect of dexmedetomidine combined with propofol for patients underwent ESD procedure was satisfactory and safe[60].

The ESD procedure of colorectal tumor is withstanding. However, this is a technical difficulty procedure. Takimoto *et al*[61] examined the efficacy and safety of dexmedetomidine sedation for ESD procedure. The 210 patients underwent the colorectal ESD were categorized into group A (continuous infusion of dexmedetomidine at 0.2 mcg/kg per hour) and group B (no administration of dexmedetomidine). A reduced blood pressure and heart rate or a decrease of oxygen saturation was not observed. The endoscopic treatment was succeeded in 100% and 82% of the patients in group A and B, respectively. The authors suggested that the use of dexmedetomidine reduced the requirement for a rescue medication and eased an endoscopic treatment. Consequently, a combination use of dexmedetomidine might establish as an effective and safe technique for the colorectal ESD[61].

Moreover, dexmedetomidine suppresses gastric motility. The use of dexmedetomidine during ESD procedure should be useful. The study of Kim *et al*[62] evaluated the safety and efficacy of the combination of dexmedetomidine and remifentanil with the combination of propofol and remifentanil for ESD procedure. Although, the efficacy and safety of these two groups were comparable, the endoscopists favored dexmedetomidine because of its action[62].

The patients with severe chronic obstructive pulmonary disease (COPD) have validated an increased risk for oxygen desaturation following the general anesthesia. The use of dexmedetomidine sedation is one of the appropriate methods for management of the COPD patients[63]. Iizuka *et al*[63] reported an anesthetic management of a 74-year-old man with severe COPD and gastric cancer underwent ESD procedure. They used dexmedetomidine under monitored anesthesia care and the patient spontaneously breathed during the procedure. The ESD procedure took 5.5 h with satisfactory analgesia, and no airway management was needed. The patient accepted the procedure and recovered well with no adverse events. Finally, the patient was discharged on the fifth postprocedural day[63].

SMALL BOWEL ENTEROSCOPY

Currently, small bowel enteroscopy is the standard method for diagnosis and treatment of small bowel abnormalities. It is a long and invasive endoscopic procedure. Anesthesia/sedation is regularly used for this endoscopy procedure[64]. The safety and efficacy of dexmedetomidine used in this procedure were investigated by the study of Sun *et al*[65]. Thirty patients with ASA physical status class Ⅰ or Ⅱ, planned for single balloon enteroscopy were randomly assigned into two groups: Group D (intravenous perfusion of dexmedetomidine 0.6 mcg/kg), and group C (normal saline of equal volume with dexmedetomidine). Group D and group C respectively received dexmedetomidine and normal saline before induction by *iv* infusion in

10 min. Then general anesthesia was induced with propofol, fentanyl and vecuronium. The maintenance of anesthesia was used by propofol in both groups. The study summarized that the use of dexmedetomidine 0.6 mcg/kg for 10 min before induction presented more stable during the period of induction. It also reduced the doses of propofol in the period of induction and operation. Dexmedetomidine could make the patient hemodynamics more stable and the recovery more rapid and complete[65].

To date, there is a wide variability of the efficacy of the use of dexmedetomidine in various GIE procedures. Several reports have been demonstrated the positive results. However, some studies did not confirm the benefits of dexmedetomidine for GIE procedures. The author also summarizes these in the two tables. Table 2 shows the use of dexmedetomidine in a single agent technique for GIE procedures including the positive and negative results. In addition, Table 1 lists the use of dexmedetomidine in a combination technique for GIE procedures including the positive and negative results.

CONCLUSION

Several sedative and analgesic drugs are commonly used in the GIE procedures. Their safety profile is dependent on their pharmacokinetic and pharmacodynamic profiles, the patient medical condition and the experience of the physician using them. Dexmedetomidine has analgesic, amnesic, sedative and anxiolytic properties. The use of dexmedetomidine as the sole anesthetic agent and as the adjuvant anesthetic agent in various GIE procedures has been published. A distinct advantage of dexmedetomidine is the maintenance of respiratory force and preserved airway patency even in the existence of rising sedation. These properties of dexmedetomidine have verified to be beneficial in high-risk patients such as the patients with OSA and COPD patients as well as the patients with extensive tracheomalacia. However, it can produce bradycardia and hypotension. Additionally, the negative results of dexmedetomidine for some GIE procedures have been happened. Therefore, further clinical investigations should to be done.

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REVIEW

Transcranial magnetic stimulation as a new tool to control pain perception

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Abstract

Treatment for chronic pain is frequently unsuccessful or characterized by side-effects. The high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) has been suggested in the management of refractory chronic pain. Various studies have shown that HF-rTMS sessions of long-duration applied at primary motor cortex induce pain relief through mechanisms of plastic changes. Efficacy of rTMS mostly depends on stimulation parameters, but this aspect requires better characterization. A rationale to target other cortical areas exists. Current data are promising, but a careful analysis of stimulation settings and maintenance treatment design are need.

Key words: Transcranial magnetic stimulation; Repetitive transcranial magnetic stimulation; Neuropathic pain; Non-neuropathic pain; Chronic pain; Neuromodulation

Core tip: The high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) is emerging as a possible approach for pain relief. The HF-rTMS delivered to motor cortex modulates brain network implicated in pain processes, facilitating descending pain inhibitory mechainsms. Current data are promising, but a careful analysis of stimulation settings and maintenance treatment design are necessary.

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INTRODUCTION

Chronic pain can be neuropathic, non-neuropathic, mixed, or without demonstrated origin[1]. Whilst acute pain is nociceptive secondary to chemical, mechanical and thermal stimulation of A-delta and C receptors, chronic neuropathic pain (NP) can persist after the initial injury because the nervous system is malfunctioning,

becoming the origin of the pain. Examples of NP are trigeminal neuralgia, postherpetic neuralgia, phantom limb pain, monoradiculopathies, complex regional pain syndromes and peripheral neuropathies. The prevalence of NP ranges from 7% to 8%[2-4]. The mechanisms involved in NP are complex and engage both peripheral and central pathophysiologic events. Several NP research studies point to different causal mechanisms including neurogenic inflammation, abnormal ectopic activity in nociceptive nerves, and impaired inhibitory modulation, defining the so-called peripheral and central sensitization[5]. Available treatments provide mainly symptomatic relief, including nonpharmacological, pharmacological, and interventional therapies[6,7]. Unfortunately, the management of NP is not easy because the response to most drugs is not univocal[8,9]. According to recent guidelines, less than 50% of the patients with chronic NP reach symptomatic benefits with drugs[6,10,11].

In this setting, neurostimulation is a promising procedure in the treatment of pain[6,12]. The techniques suggested are: Transcutaneous electrical nerve stimulation, nerve root stimulation, spinal cord stimulation, deep brain stimulation, transcranial direct current stimulation (tDCS), epidural motor cortex stimulation, and repetitive transcranial magnetic stimulation (rTMS)[6].

Specifically, TMS was first introduced in the late 1980s[13]. Initially, rTMS of the motor cortex was used to select patients for chronic stimulation by implanted electrodes[14]. It is a noninvasive method of stimulating cortical motor neurons through the scalp and skull capable of inducing electrical currents and depolarizing neurons in focal brain areas with the use of rapidly changing electromagnetic fields generated by a coil placed over the scalp[15-17]. Since then, several studies used rTMS as an investigational tool and a potential treatment for a variety of neurological and psychiatric disorders. Studies showed that rTMS provided at least partial and transient relief of chronic NP. When applied repetitively, trains of rTMS can modify cortical activity beyond the duration of the stimulation[18]. Three main aspects influence the effect of rTMS: Frequency, intensity, and duration of stimulation. In general, bursts of high-frequency stimulation ($\geqslant$ 5 Hz) lead to a facilitation of activity in the targeted brain region, whereas continuous low-frequency stimulation (about 1 Hz) provides a suppression in activity of the targeted brain region.

The rTMS produces analgesic effects activating fibres in the motor cortex and projecting to distant areas involved in pain processing[19,20]. In 2007, the EFNS produced the first guidelines on neurostimulation therapy for NP[6]. In recent years, new randomized controlled trials have published in various NP conditions. Therefore, we aimed to review all available evidence for TMS in neuropathic and non-NP, focusing the methods. A narrative synthesis was used to report the results.

TMS AND CHRONIC PAIN TREATMENT

A search of literature on the analgesic effect of rTMS in chronic pain published from 1991 to May 2015 was performed using PubMed and the Cochrane Library. Keywords included chronic pain and neurostimulation, chronic pain and transcranial magnetic stimulation, NP and neurostimulation, NP and transcranial magnetic stimulation. The present review included controlled studies with at least 10 subjects enrolled to ensure the quality of the studies. Moreover, we excluded observational studies, and only papers in English were included. To minimize possible bias, the study selection-process was carried out independently by two authors (EO, MI).

We identified 38 controlled studies, including sham stimulations, in patients with NP (spinal cord lesions, central post-stroke pain-CPSP-, trigeminal nerve lesions, peripheral nerve lesions, phantom pain, fibromyalgia and complex regional pain syndrome type Ⅱ-CRPSII-) or non-NP (migraine, CRPS type Ⅰ, low back pain, visceral and postoperative pain). Table 1 summarizes these studies. The analysis included 983 patients. Among them, 31 studies showed significant pain reduction with the high-frequency rTMS (HF-rTM) of the motor cortex (Table 1).

Unfortunately, the studies currently available have been performed on groups of patients with different kinds of NP. Evidence at medium follow-up allowing solid conclusions to be drawn is insufficient and conflicting, while evidence at long follow-up is restricted. Future studies on a large number of patients with pain due to specific diseases and the evaluation of maintainance treatment cycles should provide more certain and reproducible data.

Efficacy of rTMS in NP

Efficacy of rTMS mostly depends on stimulation parameters. When rTMS is applied in the primary motor cortex at low-frequency it is unsuccessful[21-23], while repeated sessions of long-duration (at least 1000 pulses) stimulations at high-frequency (5-20 Hz) applied over repeated sessions induce pain relief[1,24-27]. RTMS seems most effective when stimulation is focal (*i.e.*, figure-of-eight rather than circular coil)[6]. The effect starts a few days later; its duration is less than a week after a single session, 2-3 wk after consecutive sessions of rTMS[28-30]. This last aspect is the keystone for the clinical benefit[31,32]. However, this feature requires better characterization[6]. The TMS parameters vary in the studies, and it is complex to establish the best stimulation parameters to use[12]. The role of coil orientation, time of train of stimulation, inter-train interval, and number of trains, is also to definite[12].

Moreover, 22 of the 32 studies had small sample sizes, with less than 30 enroled patients, and only 16 of 32 studies recruited homogeneous populations of patients (CRPS, spinal cord injury, diabetic polyneuropathy, poststroke pain and fybromialgia), reducing

Table 1 Summary of the studies evaluating the effects of repetitive transcranial magnetic stimulation on chronic neuropathic pain and non-neuropathic pain

Ref.	Painful syndrome	Study design	Number of patients	Coil	Site stimulation	Frequency, intensity, *n* sessions	Outcomes	Efficacy
NP								
Lefaucheur *et al*[26]	Intractable neurogenic pain	Double-blind, controlled, crossover	18 (12 central NP; 6 peripheral NP)	F8	Hand M1	0.5-10 Hz 80% RMT 1	Pain intensity	Analgesic effect (only for 10 Hz)
Lefaucheur *et al*[116]	Pain due to thalamic stroke or trigeminal neuropathy	Double-blind, controlled, crossover	14 (7 central NP; 7 peripheral NP)	F8	Hand M1	10 Hz 80% RMT 1	VAS	Decrease in VAS
Rollnik *et al*[41]	Chronic refractory NP	Double-blind, controlled, crossover	12 (2 central NP; 7 peripheral NP; 2 CRPS; 1 osteomyelitis)	Double coin - Circular coin	M1	20 Hz 80% RMT 1	VAS	No effect
Lefaucheur *et al*[27]	Pain do to thalamic stroke, brainstem stroke, spinal cord lesion, brachial plexus lesion, or trigeminal nerve lesion	Double-blind, controlled, crossover	60 (36 central NP; 24 peripheral NP)	F8	Hand M1	10 Hz 80% RMT 1	VAS, thermal sensory thresholds	Analgesic effect mainly in trigeminal nerve lesions
Khedr *et al*[25]	Trigeminal neuralgia and post-stroke pain syndrome	Double-blind, controlled	48 (24 central NP; 24 trigeminal NP)	F8	Hand M1	20 Hz 80% RMT 5	VAS and the LANSS scale	Analgesic effect
André-Obadia *et al*[22]	Chronic refractory NP	Double-blind, controlled, crossover	14 (11 central NP; 3 peripheral NP)	F8	Hand M1	1-20 Hz 90% RMT 1	VAS	Analgesic effect (only for 20 Hz)
Hirayama *et al*[104]	Intractable deafferentation pain	Double-blind, controlled, crossover	20 (14 central NP; 6 peripheral NP)	F8	M1	5 Hz 90% RMT 1	VAS and SF-MPQ	Analgesic effect
Irlbarcher *et al*[117]	Chronic NP	Double-blind, controlled	27 (13 central NP; 14 phantom p)	F8	M1	1-5 Hz 95% RMT 5	VAS	No effect
Lefaucheur *et al*[15]	Unilateral hand pain of various neurologic origins	Double-blind, controlled, crossover	22 (14 central NP; 8 peripheral NP)	F8	Hand M1	10 Hz 90% RMT 1	Motor threshold at rest, MEP amplitude, CSP, ICI	ICI increase
Lefaucheur *et al*[118]	Chronic NP	Double-blind, controlled, crossover	36	F8	Face M1	10 Hz 80% RMT 1	VAS	Analgesic effect with the stimulation applied on area adjacent to the cortical representation of the painful zone
Defrin *et al*[35]	Spinal cord injury	Double-blind, controlled	12	F8	Vertex	5 Hz 115% RMT 10	VAS, MPQ, pain threshold	Increased heat pain threshold
Passard *et al*[29]	Fibromyalgia	Double-blind, controlled	30	F8	M1	10 Hz 80% RMT 10	VAS, MPQ, quality of life (Brief Pain Inventory and the Fibromyalgia Impact Questionnaire)	Decrease in VAS and better quality of life
Saitoh *et al*[115]	Intractable deafferentation pain	Double-blind, controlled, crossover	13 (9 central NP; 4 peripheral NP)	F8	M1	1-5-10 Hz 90% RMT 1	VAS	Decrease in VAS (only for 5-10 Hz)
André-Obadia *et al*[119]	Chronic NP	Double-blind, randomized, controlled, crossover	28	F8	M1	20 Hz 90% RMT 1	Pain relief, quality of life and rescue drug intake	Analgesic effect

Lefaucheur *et al*[120]	Chronic refractory NP	Double-blind, controlled, crossover	46 (23 central NP; 23 peripheral NP)	F8	Hand M1	10 Hz 90% RMT 1	Thresholds for thermal and mechanical sensations	Thermal perception improvement
Carretero *et al*[121]	Fibromyalgia	Randomized, single-blinded	28	Butterfly coil	DLPFC	1 Hz 110% RMT 20	FibroFatigue, Likert pain, HDRS, CBI	No effect
Kang *et al*[36]	Spinal cord injury	Double-blind, controlled, crossover	11	F8	M1	10 Hz 80% RMT 5	NRS, BPI	No effect
Picarelli *et al*[33]	CRPS type 1	Double-blind, controlled	23	F8	M1	10 Hz 90% RMT 10	VAS, MPQ, the SF-36, HDRS	Analgesic effect and improved quality of life
Ahmed *et al*[108]	Phantom pain	Double-blind, controlled	27	F8	DLPFC	20 Hz 80% RMT 5	VAS, LANSS scale	Decrease in VAS and LANSS scale
Mhalla *et al*[38]	Fibromyalgia	Double-blind, controlled	40	F8	M1	10 Hz 80% RMT	Pain intensity over the last 24 h, BPI, quality of life, mood and anxiety, parameters of motor cortical excitability	Analgesic effect
Short *et al*[63]	Fibromyalgia	Double-blind, controlled	20	F8	M1	14 10 Hz 120% RMT	BPI, HDRS, Fibromyalgia Impact Questionnaire	Improvement of daily pain, number of tender points, HDRS and FIQ scores
Lefaucheur *et al*[122]	Chronic refractory NP	Controlled, crossover	14 (3 localized in the face, 4 upper limb, 3 lower limb, 4 hemibody)	F8	M1	10 10 Hz 90% RMT 3	VAS	Analgesic effect
Hosomi *et al*[109]	NP	Double-blind, controlled, crossover	64	F8	M1	50 Hz 90% RMT 10	VAS, SF-MPQ, PGIC, and BDI	Analgesic effect
Onesti *et al*[28]	Diabetic neuropathy	Double-blind, controlled, crossover	23	H-coil	Vertex	20 Hz 100% RMT 5	VAS, area and threshold of RIII nociceptive flexion reflex RIII reflex	Decrease in VAS and RIII area
Jetté *et al*[34]	Spinal cord injury	Randomized, controlled, crossover	16	F8	M1	10 Hz 90%-110% RMT 3	VAS, motor mapping parameters	Decrease in VAS
Boyer *et al*[30]	Fibromyalgia	Double-blind, randomized, controlled	38	F8	M1	10 Hz 90% RMT 14	FIQ, SF-36, brain metabolism	Improvement of quality of life
Dall'Agnol *et al*[123]	Myofascial pain syndrome	Double-blind, randomized, controlled	24	F8	M1	10 Hz 80% RMT 10	Pain quantitative sensory testing, conditioned pain modulation, TMS parameters, BDNF	Analgesic effect mediated by mechanisms enhancing the corticospinal inhibitory system and BDNF
Yılmaz *et al*[40]	Spinal cord injury	Double-blind, randomized, controlled	17	F8	Vertex	10 Hz 110% RMT 10	VAS	No effect

Hodaj *et al*[124]	Chronic refractory facial pain	Open-label study	55 (19 cluster headache; 21 trigeminal neuropathic pain; 15 atypical facial pain)	F8	Face M1	10 Hz 80% RMT 12	VAS, CGIC scale	Analgesic effect
Khedr *et al*[125]	Malignant NP	Randomized, controlled	34	F8	Hand M1	20 Hz 80% RMT 10	VDS, VAS, LANSS, HDRS	Analgesic effect
Lindholm *et al*[126]	Neuropathic orofacial pain	Randomized, controlled, cross-over	16	-	S1/M1, right SII	-	NRS, BPI	Analgesic effect (only for SII)
Non-NP								
Brighina *et al*[46]	Migraine	Double-blind, randomized, controlled	11	F8	DLPFC	10 Hz 90% RMT 12	Frequency of attacks, Headache index	Significant reduction of outcome measures
Pleger *et al*[48]	CRPS	Double-blind, controlled, crossover	10	F8	M1	10 Hz 110% RMT 1	VAS	Analgesic effect
Borckardt *et al*[127]	Postoperative pain	Double-blind, controlled	20	F8	Left PFC	10 Hz 100% RMT 1	VAS for mood, opioid pump use	Reduction in opioid use
Johnson *et al*[49]	Low back pain	Double-blind, controlled, crossover	17	F8	M1	20 Hz 95% RMT 1	Detection and pain thresholds for cold and heat sensations	Increased heat pain threshold and lowered cold detection
Fregni *et al*[50]	Pancreatitis	Double-blind, controlled	17	F8	SII	1 Hz 70% RMT 10 -	VAS, BDI	Analgesic effect
Conforto *et al*[47]	Migraine	Randomized, double-blind, parallel-group	18	-	DLPFC		Number of headache days	No effect
Melchior *et al*[51]	Irritable bowel syndrome	Double-blind, controlled, crossover	21	F8	M1	20 Hz 80% RMT 5	Pressure pain threshold, changes in maximum tolerated rectal volume, rectal compliance and average pain intensity	Maximun tolerated rectal volume and analgesic effects
Avery *et al*[52]	Chronic widespread pain	Double-blind, randomized, controlled	19	-	DLPFC	- 15	BIRS	No effect

NP: Neuropathic pain; BPI: Brief pain inventory; FIQ: Fibromyalgia impact questionnaire; F8: Figure of 8 coil; H: Hesed; HDRS: Hamilton depression rating scale; ICI: Intracortical inhibition; LANSS: Leeds assessment of neuropathic symptoms and signs; MPQ: McGill pain questionnaire; PFC: Prefrontal cortex; RIII: Nociceptive flexion reflex; SF-36: 36-item short-form health survey; SICI: Short intracortical inhibition; SII: Somatosensory cortex; VAS: Visual analog scale; MEP: Motor evoked potential; NRS: Numeric rating scale; PGIC: Patient global impression of change scale; BDNF: Brain-derived neurotrophic factor; VDS: Verbal descriptor scale; CGIC: Clinical global impression of change; DLPFC: Dorsolateral prefrontal cortex; BIRS: Gracely box intensity scale.

assurance about which states are more responsive to TMS[1,28-30,33-41]. Another unsolved question concerns which site in the motor cortex gives the most effective pain relief. Stimulation is commonly delivered to the contralateral motor cortex to painful area[1,42].

Also the left DLPFC could have a function in nociceptive control, while the left prefrontal cortex has been used in rTMS studies in patients with fibromialgia[39,43] (Figure 1).

Also tDCS, a technique that elicits constant weak electric currents through the scalp throught two electrodes, is able to modulate excitability in cortical tissue. Moreover, it is important to specify that tDCS does not induce action potentials in axons, but it cause polarization of neurons changing their average level of discharge. Several studies examined the tDCS applied to the motor cortex as a possible treatment of chronic pain, but a recent meta-analysis does not suggest a significant analgesic effect of this technique[23].

The mechanisms underlying the effect of rTMS in pain are not clearly identified, but probably involve neuronal plasticity[44,45]. Therefore it is suggested that maintenance therapy for longer intervals should prolong long-lasting effects. Unfortunately, only one study to

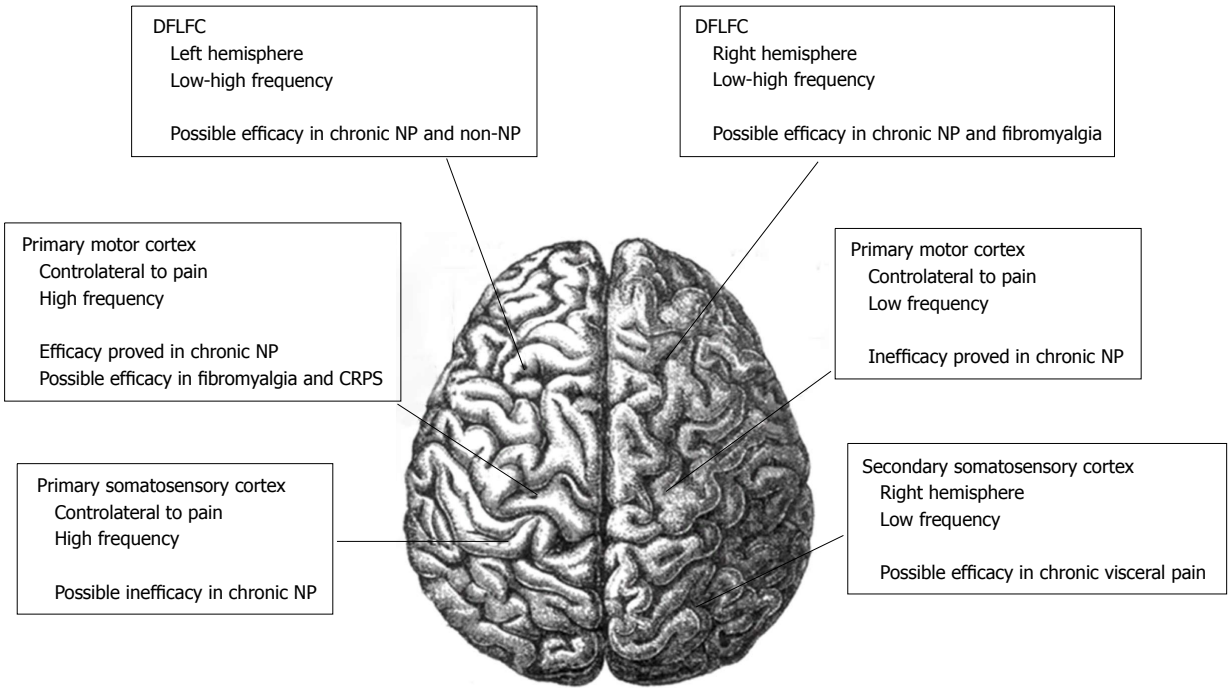

Figure 1 Analgesic efficacy of repetitive transcranial magnetic stimulation according to the cortical target. DLPFC: Dorsolateral prefrontal cortex; NP: Neuropathic pain; CRPS: Complex regional pain syndrome.

date evaluated long-term rTMS maintenance therapy[38].

Efficacy of rTMS in non-NP

In the past ten years, the rTMS have been also evaluated in different non-NP conditions[1] (Table 1).

Regarding application for migraine, active HF-rTMS delivered over the left DLPFC gave promising results but, in the absence of large controlled studies, no recommendation can be suggested[1,46,47]. Also regarding to the treatment of chronic visceral pain, low back pain and CRPS type Ⅰ with rTMS, literature is still limited, and no conclusion can be definitely drawn[48-52]. Future research in this field should specifically investigate in a large number of patients the most appropriate cortical target, and the frequency of stimulation[1]. Moreover, a specific analysis regarding to the possible effect of rTMS on other clinical aspects of these syndromes, such as affective-emotional and cognitive components is needed.

PHYSIOLOGICAL BASIS OF rTMS

Practical aspects of rTMS

In 1985 Barker *et al*[13] proposed the first magnetic stimulator for the transcranial stimulation of the human brain, giving the prerequisite for subsequent clinical use of TMS. A stimulating coil produces a brief magnetic field when an electrical pulse generator creates a discharge current of several thousand amperes. When the coil is placed on the skull of a subject, it induces an electrical field able to depolarize nerve cells and to stimulate neural networks[1]. The stimulus waveform can be monophasic or biphasic[53]. The rTMS using monophasic pulses activates an homogeneous population of neurons, while biphasic pulses tend to generate a more complex pattern of neural activation, producing local changes but also effects at distance from the stimulus site[1,54].

Site of stimulation

The first task for pain modulation is to locate primary motor cortex (M1), checking visually the muscle twitch inducing by TMS pulses[12]. Commonly in clinical settings, the intensity of the TMS should be not able to induce a motor response[12]. Specifically, TMS applied in short trains at high frequency and suprathreshold intensity over the M1 elicits a progressive increase in motor evoked potential (MEP) amplitude, demonstrating the phenomenon of MEP amplitude facilitation, through intracortical mechanisms similar to short-term synaptic plasticity[55-59].

However, a rationale for targeting other cortical areas exists. The DLPFC could have a role in nociceptive control[43]. In healthy subjects with pain induced by a capsaicin injection into their hand, the stimulation of the left DLPFC produced a significant pain relief. No improvement was noted when the right DLPFC was stimulated[60]. The effect may be related to the release of endogenous opioids by the left DLPFC[61]. Also rTMS of the cerebellum has been considered for the possible lowering in pain thresholds[62]. Moreover, The left prefrontal cortex has been used in rTMS fibromyalgia studies, but only a small analgesic effect has been noted[63].

Intensity of stimulation

The intensity of the stimulation is classically regulated for each patient to obtain the minimal intensity of

stimulation applied to M1 that evokes a motor response. It is measured according to the RMT, the lowest stimulation intensity able to generate a MEP small (50 mV) amplitude in 5 of 10 TMS pulses. In the clinical setting, stimulation intensity is frequently subthreshold (80%-90% of RMT)[64]. When the RMT is identified, rTMS is performed in bursts of stimuli ("trains") with a definite frequency[12].

Frequency of stimulation

RTMS can be carried out at low (1 Hz) or high frequencies (5 Hz). When performed at high frequencies, rTMS pulses are delivered in trains divided by specific intertrain intervals. Typically, low-frequency rTMS is considered to have inhibitory properties, whereas HF-rTMS is considered to have excitatory properties[64]. HF-rTMS consists specifically of intermittent bursts of TMS pulses able to induce a long-term potentiation of synaptic activiy, which may clarify why rTMS effects can overcome the period of stimulation[64].

Number of sessions and total number of pulses per session

A central question is whether the analgesic effect of rTMS can be prolonged by maintenance sessions performed periodically. To date, 24 of 39 studies have performed repetitive sessions of rTMS to enhance analgesic effects of a single session of stimulation, but maintenance protocol was only tested in one study[38]. Usually, the number of sessions applied range from 5 sessions to 30 sessions. The majority of studies have involved a total of 10 sessions. Based on more recent studies, a general trend indicates a greater number of sessions (> 10) associated with more persisting improvement in pain perception (Table 1).

The total number of pulses in each rTMS session seems related to the analgesic effect, but it is not clear whether a minimum number of pulses is required to obtain the clinical outcome. Usually this value ranges between 1000 to 2000[1]. Moreover an important safety parameter as the intertrain interval (the time in between trains of pulsed energy when no stimulation is occurring) is usually about 10 s[1].

Coil

Coil design and orientation are important. The "figure-of-eight" coil is able to induce a focal magnetic field stimulating only superficial cortical regions of the brain[12]. Other novel models are the Tilted double-coil and the Hesed (H)-coil, which drop at a depth of about 6 cm[12]. Specifically, the H-coil lets deep brain stimulation without significantly increasing induced fields in superficial cortical regions, therefore preventing the risk of adverse effects[65,66]. rTMS with the H-coil has already proved effective as an acute treatment for major depressive disorder, bipolar depression, schizophrenia and post-traumatic stress disorder[65,67-69]. Furthermore, there are ongoing studies of its use to treat a very wide range of neurological, psychiatric and medical conditions, including NP[28].

Placebo rTMS

Placebo effects need to be better reported[25]. Theoretically, ideal placebo rTMS should be characterized by the same subjective somatic scalp sensation and the acoustic artifacts compared to active coil, and no physiological effect on the targeted cortical region[70]. In the early research, placebo was considered a coil placed in a different area from zone stimulated in the active condition, or a coil oriented with an angle of 45-90 grades on the scalp instead of tangentially[1]. These solutions are not the most reliable, because the stimulation site could be perceived by the subject, or the sham location could cause unexpected effects[1,71]. In the last decades, sham coils have been projected and commercialized in order to block the magnetic field provided, and to produce auditory artifacts and scalp sensation equivalent to that of a real coil[72,73]. Although this stimulation ideally seems a perfect placebo, the cutaneous sensation remains different in about half of the cases, especially when the stimulation intensity is high[72,74].

CONSIDERATIONS ABOUT MECHANISMS OF ACTION OF rTMS

Although the TMS acts on the superficial cortex, the generated action potentials propagate influencing distant neural networks[12]. The M1 contains pyramidal cells that give rise to numerous excitatory corticospinal projections. Most of These projections are oriented perpendicularly to the brain surface. rTMS applycated on the M1 modulate the cortical excitability producing changes in the following physiological parameters: MT, MEP, silent period, intracortical facilitation, and intracortical inhibition[75]. In chronic pain, the involvement of M1 projections to pain-modulating structures has been demonstrated[23]. Moreover, a rationale for targeting other cortical areas exists. The DLPFC is a cortical target used in studies on major depression, and it is considered to have a function also in nociceptive control[43,61,76]. HF-rTMS on the right DLPFC has shown analgesic effects similar to M1 stimulation[46,77]. Furthermore, left DLPFC stimulation should induce an improvement of pain perception in a model of acute pain[43,78]. The left prefrontal cortex has been used in rTMS studies in patients with fibromyalgia, but it has shown a minor analgesic effect[63].

rTMS seems to modulate cortical plasticity, referred to as the functional reorganization of the inter neuron connections and neuronal properties. Inhibition of the gamma-amminobutyric acid (GABA) pathways produces cortical excitation, rather than a direct enhancement of motor cortex excitability[79-82]. On the other hand, low-frequency rTMS could increase the inhibitory corticospinal control, perhaps through GABA-B

transmission, prolonging the CSP duration[1,83-86]. The changes in synaptic plasticity brought by rTMS are explained by long term potentiation (LTP) and long term depression (LTD)[44]. LTP is induced by high frequency stimulation and LTD by low frequency stimulation. The LTP is mediated by the post-synaptic N-methyl-D-aspartate (NMDA) receptors, that lead to calcium flux into the post-synaptic neuron when activated[45]. Calcium activates enzymatic changes in pre- and post-synaptic neurons, increasing the synaptic activity. It also induces the expression of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors on the postsynaptic neuron, increasing the cells sensitivity to glutamate[87]. Furthermore, LTD is characterized by depression of the synaptic transmission, depending on the modulation of NMDA receptors with the reduction of calcium influx, and the internalization of AMPA[87].

The long lasting effect of rTMS (late-LTP) is thought to be exercised by gene induction and protein synthesis[87]. Gene expression has resulted in increased synthesis of c-fos mRNA in the thalamus and parietal cortex, and BDNF mRNA in the hippocampus and parietal cortex[88-90]. Considerable evidence from HF-rTMS studies suggests that short-term synaptic plasticity happens at cortical rather than spinal level[91-94]. When rTMS is delivered in human subjects, the amplitude of the MEP and the duration of the CSP increases during the train[55,75,95-100]. The MEP facilitation also persists after the train ends, and it is probably due to the recruitment of cortical excitatory interneurons[55,75,92,94,99]. It is influenced by the number of stimuli in the train, being greater with longer (20, 40 and 60-stimuli), suggesting mechanisms of short-term synaptic enhancement[59,101].

rTMS has also been found to modulate the activity of brain neurotransmitters, reducing dopamine in the frontal cortex and increasing its levels in the striatum[102]. Moreover, serotonin levels increased in the hippocampus[102]. All these aspects may explain why different rTMS protocols are effective or not, depending on various parameters of stimulation. Further, age, and genetic features could influence the clinical effect of rTMS, with heterogeneous therapeutic responses[1,103].

LIMITATIONS OF rTMS IN PAIN TREATMENT

The results of studies exploring the effects of rTMS on pain are positive but still inconsistent, because of small samples of patients, differences in the TMS methodologies, heterogeneous populations of patients and lack of maintenance protocols. In a Cochrane Review of 2013, a short-term effect on pain of HF-rTMS applied to M1 was confirmed[23]. Moreover, a detailed study to determine which are the best stimulation parameters, is targeted. Studies on image-guided navigation to perform rTMS of M1 in pain patients have provided evidence that the analgesic effect of rTMS links with the integrity of the thalamocortical tract[1,104,105]. Unfortunately, objective indicators of perceived pain, including MEP and RIII, were considered in only two studies neurophysiological[15,28]. New extended studies should improve knowledge in this field of research.

Further rigorously designed studies, particularly of longer courses of stimulation applied on large population of patients, are required to address the issue. Future evidence may significantly confirm the current results. The main question is whether the clinical effect could indeed improve the management of patients with chronic pain in daily clinical practice.

FUTURE RESEARCH DIRECTIONS

The conclusions of our analysis, related to the actual literature data on rTMS for chronic pain, match with those suggested in previous reviews and meta-analyses[1,6,17,23-25,32,106]. rTMS has become a promising therapeutic tool for a variety of neurological and psychiatric diseases[107]. Different types of NP respond to rTMS, and this is producing a fast growth in researchers interested in rTMS for clinical purposes[6,26,108-110]. Unfortunately at the current time in the lack of large studies, only careful recommendations of rTMS can be suggested[1,6]. The efficacy of a single HF-rTMS session persists for some days, and it could extend with the repetition of sessions[1]. Moreover, the best stimulation settings may be yet to determined.

Studies including neurophysiological evaluation of the effects of the cortex TMS in other brain regions through the use of imaging and electrophysiologic techniques (such as electroencephalography, magnetoencephalography, MRI navigated TMS) could add value at the understanding of the mechanism of action of this technique[111]. New TMS machines have allowed the administration of pulses more focally and at higher frequencies. Moreover, frameless stereotactic systems, have been developed, permitting the identification of specific location in the desired brain target and the precise and comparable placing of the coil during different TMS sessions[112-114].

In future, therapeutic studies need to define the correct utilization of rTMS in the clinical practice for chronic pain, above all if the long-term effect exists. Moreover, studies of rTMS in other diseases associated with chronic pain, such as osteoarthritis, bladder pain syndrome and post-stroke pain, could be of interest. Finally, if rTMS becomes a proven method for the treatment of chronic pain, the development of a home-based rTMS system will be necessary[115].

Active research in pain is still taking place and has the potential to provide useful data (31 open studies on TMS and pain on https://clinicaltrials.gov). Based on this new research, novel therapeutic guidelines may be established in future. Apart from its potential clinical role, rTMS is a valuable probe of brain function that can be used to investigate the neural circuitry. This additional knowledge might help in the development of new treatments. rTMS is non-invasive and can be

applied to any patient with drug-resistant NP who could be aspirant for the insertion of a cortical stimulator. In addition, further studies using maintenance sessions of rTMS and evaluating the multiple features of chronic pain are needed to give a more solid basis for its clinical applications.

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MINIREVIEWS

Insight into orthodontic appliance induced pain: Mechanism, duration and management

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Abstract

Most of the orthodontic patients experience pain during treatment and this significantly influences their attitudes and the approach towards treatment. A number of factors that influence pain response include age, gender, personal pain threshold, mood and stress level of the person, cultural differences and types of orthodontic treatment. Pain is a often overlooked subject by orthodontists, it is nevertheless important to understand the source and mechanism of the pain that occurs during treatment, as well as the methods for managing and controlling this pain. This review attempts to overview the mechanism, duration and current management strategies of orthodontic treatment.

Key words: Orthodontic appliance; Pain mechanism; Orthodontic treatment; Pain; Pain management

Core tip: Pain during orthodontic treatment is an important concern for both clinicians and patients. Although it is not possible to completely eliminate pain during orthodontic treatment, it is still necessary to understand its causes and to minimize it to the greatest extent possible.

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INTRODUCTION

Pain is a commonly encountered sensation in daily human life that is usually difficult to describe or diagnose, and which often represents an important problem that must be addressed through a multidisciplinary approach encompassing all branches of medicine.

Pain during orthodontic treatment is an important concern for both clinicians and patients[1,2]. Patient motivation and cooperation is an important factor in orthodontic treatment, while pain significantly influences

patient attitudes and the approach towards treatment. Studies indicate that 90% of orthodontic patients experience pain during treatment, and that 30% consider discontinuing or interrupting their treatment due to pain[3,4].

The study of Abu Alhaijaa *et al*[5] evaluated the relationship between personal characteristics, expectation of pain, and treatment compliance, reporting that individuals who experienced less pain during treatment generally displayed a more positive attitude, and that those sufficiently informed about treatment procedures had less expectations of pain.

In another study, 95% of the patients reported that they experienced pain in different stages of their treatment, and that this inevitably affected their diet[6].

For these reasons, although pain is a subject that is often overlooked by orthodontists, it is nevertheless important to understand the source and mechanism of the pain that occurs during treatment, as well as the methods for managing and controlling this pain.

Mechanism of pain

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Pain also has a strong motivational component, in that it not only triggers a withdrawal reflex, but also induces a highly organized avoidance and evasive behavior[7]. The motivational aspect of pain is an essential function, without which it would be difficult - if not impossible - for the human body to protect and sustain itself[7].

In orthodontic treatments, the force transmitted by appliances allows the movement of the teeth within the alveolar bone[8]. However, this movement also has the effect of causing the compression and inflammation of the blood vessels and nerves within the periodontium. The perception of orthodontic pain is associated with changes in blood flow that occur due to inflammatory reactions following the application of force[9]. Studies indicate that periodontal pain consists of a combination of pressures, ischemia, inflammation, and oedema[10]. Davidovich and Shanfeld have reported that the application of force leads to acute inflammation, which, in turn, results in periodontal vasodilation and the sensation of pain[11]. It is known that the development of hyperalgesic resistance is associated with the release of various chemical mediators[12,13]. Studies have shown that the chemical mediators involved in the development of the hyperalgesic response include histamine, substance P, encephalin, dopamine, serotonin, glycine, glutamate gamma-amino butyric acid, prostaglandins (PGs), leukotriene, and cytokines[9,12,13]. The studies in the literature concerning the increase in the level of these mediators have also demonstrated that the hyperalgesic response occurs following the application of force[9,14,15]. Recent studies have investigated the molecular basis of orthodontic pain by evaluating subjects such as the elevation in the level of various neuropeptides[9].

Kato *et al*[16] previously investigated in rats the distribution of the neurofibrils within the PDL [such as the neurofilament protein (NFP), calcitonin gene-related peptide (CGRP), vasoactive intestinal polypeptide and neuropeptides Y] following the application of force on the first molar. Three days after the application of force, they observed that the level of neurofibrils consisting of NFP and CGRP increased in both the compressed and strained sides, and that these levels returned to normal on the 14th day[9,16].

Studies indicate that substance P - a sensory neuropeptide released from the peripheral nerve ends - and CGRP both regulate the secretion of proinflammatory cytokines released by monocytes, such as IL-1β, IL-6, and TNF-α[15,17,18]. Yamaguchi *et al*[19] determined that the level of three major cytokines (IL-6, IL-8, and TNF-α) released from the human dental pulp cells increased significantly in the 12 h following the application of mechanical force. They also reported that major neuropeptides, such as proinflammatory cytokines, might be involved in pulpal inflammation during orthodontic teeth movement.

Duration of pain

The time of onset and duration of orthodontic pain was similar in most studies, with patients generally beginning to experience discomfort four hours after the application of orthodontic force[20]. In a study using the Visual analogue scale (VAS) to evaluate the level of pain that developed following the placement of separators, the highest intensity of pain was observed on the second day, while the pain fully subsided by the fifth day[21]. Nearly half of the patients evaluated during this study were compelled to change their diet habits and to use analgesics.

In a study using the VAS to evaluate pain in patients with arch wire and separators placed between their molars, Wilson *et al*[20] reported that pain generally began four hours after the application of force, reaching its highest level 24 h later, and almost fully disappearing by the seventh day. On the other hand, Tuncer *et al*[22] described that pain began two hours following the application of orthodontic elastics, reaching its highest level six hours later, and almost fully disappearing by the second day.

A previous study reported that although pain ended in most patients on the seventh day following the application of orthodontic force, 25% of the patients still continued to experience a certain level of pain[23]. The results of the said study indicated that orthodontic pain began two to six hours following the application of orthodontic pain, reaching its maximum level within the first two days, and then gradually decreasing until it completely disappeared by the seventh day.

FACTORS AFFECTING ORTHODONTIC PAIN

Pain is a subjective finding, and different individuals may

display different pain responses to the same stimulus. There are a number of factors that are responsible for these differences in response. The main factors that influence pain response include age, gender, personal pain threshold, mood and stress level of the person, as well as cultural differences and the person's previous pain experiences[1,4,9,24,25].

Age

As orthodontic treatments generally involve different therapeutic procedures for different age groups, making comparisons regarding the effect of age is difficult, with studies on this subject generally providing somewhat contradictory results. However, Ngan *et al*[26] previously reported that there were no statistically significant differences between adolescents and adults regards to pain. On the other hand, in their comprehensive and large-scale study on pre-adolescents, adolescents, and adults, Moerenhout and Brown[27] reported that adolescents exhibited higher levels of pain.

In recent years, there is a growing consensus that the relationship between pain and age should be evaluated by also taking into account the effect of age, since this relationship appears to be particularly affected by adolescence. Sandhu and Sandhu[28] determined in their study that girls between the ages of 14 and 17 experienced the highest levels of pain during orthodontic treatments. These authors emphasized that due to their synergistic interaction, the effects of age and gender on the level of pain during orthodontic treatment should be evaluated together rather than separately[28].

These contradictory and conflicting results appear to stem not only from the fact that different orthodontic treatment methods are generally used for different age groups, but also from the fact pain is a multifactorial element that can be affected by gender differences, as well as the psychological and emotional state of the patients.

Gender

Similar to age, gender is another factor that is unlikely to provide accurate assessments when used independently to evaluate pain. This is because even within the same gender, factors such as age group and cultural differences can significantly affect the level of pain that is experienced. Certain studies report that while there are no statistical differences between males and females within the 11-14 age group, a significant difference begins to be observed within the 14-17 age group. This change is reported to be associated with the hormonal changes experienced by females during adolescence[28,29]. Cultural differences similarly appear to cause significant variations in study results regarding the relationship between pain and gender. In a study evaluating the pain response of both male and female individuals, it was observed females generally found it easier to express and describe the pain they experienced compared to males[30]. These contradictory results indicate that the perception of pain is affected not only by physiological differences, but also by cultural factors[31].

Although certain studies evaluating the effect of gender on orthodontic pain describe that females exhibit higher levels of pain than males[6,32,33], most studies from the orthodontics literature have not identified a gender-related difference in the perception of pain[34-37].

Emotional state

Dental anxiety ranks fifth among the objects and situations that are the most common sources of anxiety[38]. A study conducted by Hamurcu[39] compared the intensity of pain experienced with their level of anxiety, and determined that patients exhibiting higher anxiety scores also experienced more pain.

In a study comparing the level of pain experienced by patients at the beginning of orthodontic treatment with their personal characteristics, Bergius *et al*[40] determined that individuals with dental anxiety experienced higher intensities of pain. A similar study observed that anxiety reduced the pain threshold, causing patients to perceive even the simplest procedures as painful[41].

THE EFFECT OF THE TYPE OF ORTHODONTIC TREATMENT ON PAIN

Orthodontic separation

Orthodontic separation is a method applied prior to the placement of an orthodontic band, and is usually associated with significant pain for the patients[9,21,26,42]. In another study performed on 55 patients, 87% of the patients described pain following the placement of an orthodontic separator, while 72% required analgesics[37]. In a study evaluating motor and sensory changes following the placement of a separator by using an electromyograph (EMG), Michelotti *et al*[43] observed a decrease in the pain threshold and motor output of the chewing muscles, and suggested that this was a protective mechanism to prevent further damage to the injured area.

Dental archwire placement and activation

The pain that develops following the initial placement of an archwire has been the subject of numerous studies. These studies generally report that most patients begin to experience pain four hours after the application of the arch, with the level of pain reaching its peak within the first 24 h, and then gradually decreasing[6,26,32,34,42,44,45].

No statistically significant differences have been identified between the perception of pain and the intensity, prevalence, and duration of the archwire usage[34,46,47]. In a study comparing the super-elastic nickel titanium wires with helical stainless steel wires, Sandhu *et al*[48] reported no statistically significant differences in the level of pain experienced with these two wires. However, they suggested that the super-elastic wire caused more pain during the hours when the level of pain reached

its peak (between the 12th and 24th h), and that was probably due to the greater force applied by this type of wire. Although the current literature indicates that the application of either strong or weak forces by the wires does not lead to a significant difference in terms of the resulting level of pain, Sandhu's study nevertheless suggests that higher forces result in higher IL-1 beta concentrations, and that this engenders a difference in the level of pain observed during the peak period[48]. Ogura *et al*[49] similarly performed comparisons between weak and strong forces, and determined that during the period of maximum pain levels, biting while the teeth were exposed to stronger forces lead to higher levels of pain.

Previous studies evaluating the activity of chewing muscles following arch activation by using EMG identified a decrease in the masseter muscle activity, which is believed to be responsible for the reflex mechanism for avoiding harmful stimuli[50-52]. Murdock *et al*[44] and Erdinç *et al*[34] have reported that patients report greater pain in the posterior teeth than their anterior teeth during the leveling stage and chewing. In sum, most studies indicate that arch placement and activation can lead to pain, and adversely affect the daily activity and diet habits of patients[9].

Type of appliance

The level of pain caused by different types of appliances during orthodontic treatments has been evaluated in many studies. In studies comparing fixed and removable appliances, Oliver and Knapman[1] identified no significant differences between these two types of treatments, while Sergl *et al*[25] and Gianelly *et al*[53] reported that treatment with fixed appliances resulted in greater pain.

Various comparisons have been performed between fixed orthodontic treatments applied using different methods. Wu *et al*[54] and Caniklioglu *et al*[55] have performed comparisons between labial and lingual appliances, and reported no statistically significant difference with regards to the total level of perceived pain associated with these appliances. However, they also described greater pain on the tongue among patients who received lingual appliances, as well as greater pain on the lips and cheeks among patients who received labial appliances[54,55]. A recent study compared the application of a fixed labial appliances with the Invisalign® and determined that Invisalign® caused less pain[56].

Shalish *et al*[57] have evaluated and compared the fixed lingual treatment, fixed labial treatment and Invisalign® treatment in adult patients, and determined that the most pain and general oral dysfunction occurred in the lingual apparatus group; that Invisalign® caused significant pain in the first day of treatment; and that Invisalign® was similar to conventional labial techniques in terms of general oral dysfunction[57].

Bertl *et al*[58] have examined self-ligating brackets and conventional brackets with respect to pain, and determined that self-ligating brackets caused significantly more pain. In contrast to Bertl *et al*[58], Tecco *et al*[59] suggested that conventional brackets lead to stronger and more persistent pain, while self-ligating brackets tended to cause pain mainly during chewing and biting.

Orthopedic forces

The main purpose of craniofacial orthopedics is to bring skeletal changes by applying significant forces to the craniofacial complex. Various publications report the occurrence of pain during rapid palatal expansion applied for the transversal skeletal development of the maxilla[60-62]. In such cases, patients generally describe a sensation of pain spreading across the craniofacial area[9].

Headgear applications represent another treatment method used during the development stages of children to bring about skeletal and dental modification. Studies have demonstrated that patients with such appliances generally begin to experience pain approximately 24 h after initial application, with the sensation of pain and discomfort gradually decreasing after the 3rd day[63,64].

Egolf *et al*[65] have reported that nearly 28% of patients using orthodontic elastics and headgear discontinue to wear them due to pain. Ngan *et al*[64] previously examined the chewing muscles of protraction headgear patients by using EMG, and determined that the pain associated with the orthopedic devices originated not from the muscle tissues, but instead from the acute inflammation caused by the accumulation of forces in the sutural areas.

Skeletal anchorage systems

Recently, skeletal anchorage systems are being used for absolute anchorage. These devices can be grouped/classified as "mini-plate" and "mini-screws". Zawawi[66] reported that patients with mini-screw implants reported significantly less pain; that 32.5% of patients receiving mini-screw implants did not require any medication; that 59.1% of these patients only required a single-dose analgesic; and that patients generally preferred mini-screws instead of extraction.

Kuroda *et al*[67] previously compared the level of pain experienced with mini-plate and mini-screws. No significant differences were observed in terms of perceived pain levels between mini-plates and mini-screws inserted through incisions, while a significant difference was observed when mini-plates and mini-screws were implanted without using incisions, with the mini-plates resulting in noticeably more pain[67]. In agreement with Kuroda *et al*[67]'s findings, Kawaguchi *et al*[68] demonstrated that implanting mini-plates without using incisions resulted in three times greater pain than placing mini-screws without incisions. The abovementioned studies have generally suggested that the main causes of pain during the application of skeletal anchorage systems could mainly be associated

with sutures, periosteal separation, and incisions.

Debonding

Many patients also describe pain when removing their fixed appliances. Various studies have shown that applying intrusive forces during the debonding of fixed appliances reduced the level of pain experienced. These studies have therefore recommended applying finger pressure, biting a cotton roll, or using an occlusal wax layer during the removal process in order to reduce pain[69,70].

PAIN MEASUREMENT

It is important that pain is measured by the use of standardized pain scales and by using common language due to its complex and subjective nature. Unfortunately, objective assessment methods are still developing and subjective assessment is still the commonly used method. As the pain perception varies among individuals, it is important to take the patients' own report into consideration. Ideally, a pain intensity scale must have a low rate of incorrect responses, should be easy to administer, and be sensitive with an adequate number of response categories and be statistically powerful to detect treatment effects.

VAS is considered to be superior to other pain scales in terms of reproducibility and ease of measurement. VAS is a numeric scale and consists of a horizontal or vertical 100 mm line that has "no pain" and "worst pain" labels on two endpoints; the patient is asked to mark on the line to show the degree of pain experienced. The distance between the low end of the scale and the patient's mark is used as the index of pain intensity[8].

MANAGEMENT AND CONTROL OF ORTHODONTIC PAIN

Although it is not possible to completely eliminate pain during orthodontic treatment, it is still necessary to understand its causes and to minimize it to the greatest extent possible. It is therefore important to take into consideration and avoid overlooking the patient's complaints during the treatment process, and to inform them beforehand about the pain the treatment may cause. A study performed by Krukemeyer *et al*[4] determined that orthodontists tend to ignore or dismiss the pain caused by the treatment, and that they generally expect a lower level of pain and medication use than the level reported by patients. Krukemeyer *et al*[4] also reported a general lower-than-necessary amount of medication use. Abu Alhaijaa *et al*[5], on the other hand, reported that patients sufficiently informed about the treatment process had a lower medication requirements.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are usually the medication of choice in orthodontics to alleviate mild and moderate pain and inflammation, although there is no standard protocol concerning the application of NSAIDs. Many drugs such as acetaminophen, ibuprofen, aspirin, and flurbiprofen have been used and determined to be effective in the management of orthodontic pain[71-76]. However, a number of previous studies have suggested that PGs, and especially prostaglandin E2 and prostaglandin E1, can affect bone remodeling and teeth movement[14,77-80]. Nevertheless, the general consensus in orthodontic pain management is that the application of a low-dose analgesic during the first days of treatment will not have a clinically significant effect on the movement of the teeth. Another point that needs to be taken into consideration during orthodontic treatment is the possibility that teeth movement might be affected in patients who have been regularly receiving NSAIDs for a long period of time due to a systemic condition. In such cases, acetaminophen should be preferred because it provides sufficient analgesia without affecting teeth movement[8].

In recent times, there has been an increasing focus on preventing the development of a pain memory through preemptive drug administration. Steen Law *et al*[76] previously assessed the effect of ibuprofen and placebo administered one hour prior to separator application, and determined that the ibuprofen administration significantly reduced the pain experienced by the patients. Polat and Karaman[72] similarly conducted a comprehensive study evaluating the administration of five different medication (placebo, ibuprofen, flurbiprofen, acetaminophen, naproxen sodium, and aspirin) one hour before and six hours after bracketing procedures. The lowest pain scores were observed in the naproxen sodium and aspirin groups, while the highest pain scores were observed in the acetaminophen group[72]. In another study of the same authors, a single preoperative dose of placebo, ibuprofen and naproxen sodium was applied, and - in agreement with the findings of their previous study - lower levels of pain were reported during the first day in the naproxen sodium group. However, the authors also described that a single-dose application was not sufficient, and that additional postoperative doses were also necessary[42].

Non-pharmacological methods used for pain management include transcutaneous electrical nerve stimulation (TENS), laser applications, vibration, and chewing apparatuses. Profitt described that the use of chewing gum or biting blocks during application would help reduce pain[81]. This theory was investigated by Mohri *et al*[82] by evaluating the relationship between chewing and the serotonergic (5-HT) neurons responsible for nociceptive transmissions. Mohri *et al*[82] determined that the rhythmic behavior of chewing indeed suppressed the nociceptive response. Hwang *et al*[83] similarly determined that biting blocks reduced pain in 56% of their patients; however, they also observed that in other patients, biting blocks had the effect of increasing the experienced pain. Murdock *et al*[44], on the other hand, compared the effect of analgesics and

biting blocks, and determined that these apparatuses were as effective as analgesics, and that they represent a good option for adolescents.

Laser - a highly popular technological application in recent times - is also being used in the management of orthodontic pain. Fujiyama *et al*[84] reported that CO_2 laser applications are able to reduce orthodontic pain without affecting teeth movement. In another study, comparisons were performed between a low-energy gallium-arsenic-aluminum laser (LLLT) group, a placebo group, and a control group following the implantation of an arch wire. The study determined that the LLLT and placebo groups both experienced significantly less pain, although the difference between these two groups was not significant[85]. Although numerous alternative, non-pharmacological methods are being used for the management of orthodontic pain, it is known that pharmacological methods still represent the most effective approach.

CONCLUSION

Although it is not possible to completely eliminate pain during orthodontic treatment, it is still necessary to understand its causes and to minimize it to the greatest extent possible. It is therefore important to take into consideration and avoid overlooking the patient's complaints during the treatment process, and to inform them beforehand about the pain the treatment may cause. During pain management, medication that ensures the maximum reduction of pain with the minimum side effects should be administered by employing the most effective methods. In particular, the decision regarding the choice of medication or approach for reducing pain should not be left to the patient's relatives. Although there are no controlled studies supporting low-energy laser and TENS applications, further studies and growing interest on these techniques might eventually bring a new dimension to orthodontic pain management.

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Improvised technique for measuring tracheal tube cuff pressure

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Author contributions: Flores-Franco RA wrote this letter and created the described improvised technique.

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Abstract

We agree with the editorial published by Feng *et al* concerning the insufficient routine monitoring of tracheal tube cuff pressure (TTCP) by anesthesiologists, and propose an improvised technique that can facilitate and promote such routine monitoring by intensive care staff who attend to patients receiving mechanical ventilation. Insufficient monitoring of tracheal cuff pressure has also been documented for intensive care unit nurses. Measurements of cuff pressure are beneficial when used in management of air leakage around an endotracheal tube, and can be easily obtained with the aid of a personalized and simple technique performed using materials that are readily available in all hospitals. Other investigators have previously demonstrated the usefulness of employing an improvised technique. We considered that possible disadvantages are similar to those encountered when using standardized equipment. With our improvised technique, we seek to promote among the nursing staff the determination of the TTCP in intubated patients to reduce the risk of related medical complications.

Key words: Endotracheal tube; Mechanical ventilation; Cuff pressure; Improvised devices; Nursing practice

Core tip: This letter to the editor supports an opinion expressed in an article recently published in the *World Journal of Anesthesiology*. In that article, Feng *et al* mentioned that despite evidence suggesting its benefits, anesthesiologists often do not measure a patient's endotracheal tube cuff pressure. We suggest an improvised and personalized technique that can be employed to facilitate taking such measurements on a routine basis in the setting of an intensive care unit with limited resources.

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TO THE EDITOR

We read with great interest the editorial written by Feng

Figure 1 Simple and practical technique used for determining endotracheal tube cuff pressure at our institution.

et al[1], which stated that despite evidence supporting the benefits of monitoring tracheal tube cuff pressure (TTCP), such monitoring is not routinely performed in clinical practice. We support the point of view expressed by those authors, and believe it would be also applicable when monitoring patients in intensive care units (ICUs). Surveys performed in other centers have revealed that approximately 50% of nurses working in adult ICUs do not routinely determine TTCP, even when an audible air leak is detected[2]. Unlike air leakage resulting from structural damage, air leakage accompanied by normal or elevated TTCP can result from partial tracheal extubation, inadvertent intratracheal placement of the gastric tube, high mean airway pressure or a discrepancy between diameters of the endotracheal tube and trachea[3].

The high cost and limited availability of equipment specifically designed to measure cuff pressure makes such measurements difficult to perform on a routine basis in our ICUs. To overcome this problem, we have designed a simple technique for measuring cuff pressure that can be performed with readily available materials. When using this technique, a 1 mL syringe is interposed between a blood pressure manometer and the pilot balloon of the endotracheal tube (Figure 1). Optionally, a 3-way stopcock can also be interposed to add or remove air, and achieve the desired pressure level.

An additional advantage of this technique is that the required materials can be easily disposed of after their use, and thus the risk of transmitting an infection is minimized. On the other hand, one possible disadvantage is that a small loss of air volume may occur while handling the pilot balloon; however, this can also occur when using more expensive equipment.

The effectiveness of using an improvised technique to determine TTCP has previously been demonstrated by other authors, who reported results comparable with those achieved when using standard equipment, and even better results than those achieved using the pilot balloon palpitation technique[4]. Thus, we believe that our simple and practical method may strengthen protocols which call for measurements of TTCP in hospitals with limited resources.

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