Study Protocol and Statistical Analysis Plan (SAP)

USE OF DEXMEDETOMIDINE DURING CAROTID ENDARTERECTOMY: SAFETY PROFILE, AND SATISFACTION OF THE PATIENT AND OPERATORS

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Version II of 08.11.2020

INTRODUCTION

Cervical plexus block provides anesthesia and analgesia for head and neck surgery [1-7], and this block is mainly performed for carotid endarterectomy (CEA) surgery [8-12]. The nomenclature of cervical plexus block is complex, and the classification follows the anatomical topography of the structures [13]. CEA surgery is the most frequent vascular surgery in the world, and represents the most effective medical approach in significantly reducing the risk of ischemic stroke in patients with high-grade carotid stenosis [14-18]. Recently, the GALA trial did not demonstrate the superiority of general or locoregional anesthesia in this type of intervention [19-21], with notable differences between the two techniques [22], including the risk of postoperative cognitive deterioration [23].

The intermediate cervical plexus block currently represents the gold standard, compared to the intermediate cervical plexus or the cervical epidural [24, 25], although new promising techniques are gaining ground such as the anterior approach [26], or the so-called C2-C4 compartment block [27].

Dexmedetomidine is a well-known superselective α2 agonist drug, with hypnotic, sedative, anxiolytic, sympatholytic and analgesic activity, suppressing the neuronal noradrenergic storm at the locus coeruleus [28], without inducing respiratory depression [29]. Dexmedetomidine has no rebound effects even after 24 hours of continuous infusion, therefore it is well suited to administration for short-duration procedures [30]. In association with other anesthetic drugs it reduces the dose required in the perioperative period. It has a good safety margin, especially in expert hands [31]. It has been shown to have the possibility of reducing the dose of Morphine required in the postoperative period [32], decreasing PONV in laparoscopic surgery [33], and its manageability has meant that it is used

in outpatient ophthalmological surgery, gynecological surgery and intubation with optical fibers [34-38].

It has been observed that the anteroposterior diameter of the pharynx at the level of the soft palate decreases after administration of Propofol alone [39], with associated motor dysfunction [40], while Dexmedetomidine amplifies it in patients with OSAS [41] and Dexmedetomidine is associated with a lower number of apneas during sedation in patients under subarachnoid anesthesia [42]. Better pain control and peripheral oxygen saturation level has been evaluated with Dexmedetomidine instead of Midazolam [43], at different doses (1y/kg for 15 minutes followed by 0.2 y/kg) were burdened by serious adverse events such as extreme bradycardia [44]. In another study, the infusion of Dexmedetomidine 1y/kg for 10 minutes plus Midazolam was evaluated without differences in alterations of vital functions, but with a decreased satisfaction of the patients at the end of the examination [45].

The implementation of Dexmedetomidine in the Vascular Surgery room could represent an additional weapon for the safety of the Patient undergoing Carotid Endarterectomy (CEA). In a randomized-controlled study (RCT) on 64 patients undergoing CEA, the infusion of Dexmedetomidine at 1y/kg in 10 min, and then 0.2 y/kg/h, decreased the need for Urapidil and Fentanyl compared to the placebo group [46]. An RCT on 66 patients has shown that Dexmedetomidine during CEA decreases plasma levels of norepinephrine, fluctuations in sedation levels and the requirement for B-blockers in the intraoperative period [47], while another RCT shows a lower requirement for antihypertensives and analgesics in the group treated with Dexmedetomidine compared to the group treated with Fentanyl and Midazolam, but with a superiority that is not statistically significant [48]. In another retrospective study conducted by Do W et al, however, a lesser haemodynamic instability was seen in the group subjected to cervical plexus block + Dexmedetomidine compared to the group subjected to General Anesthesia [49].

Given the variability of the responses of vital parameters and dosages used in the literature, it would seem that there is not yet an “optimal dose” that can be used during CEA surgery. The positive data

suggest that it is a drug of great utility in this area, but the use at sedoanalgesic doses, i.e. as when it is used in intensive care, does not seem to be suitable for environments such as the Operating Room. Furthermore, the level of satisfaction of the three main figures operating in the Operating Room (Patient, Anesthetist and Surgeon) in relation to the type of sedoanalgesia adopted has rarely been studied.

The aim of this study is therefore to evaluate the safety of the use of the two anesthesiological techniques, and the response of the Patient, the Anesthetist and the Surgeon based on sedoanalgesia with Fentanyl + Midazolam, or with Dexmedetomidine.

AIM OF THE STUDY

OBSERVATIONAL LONGITUDINAL COHORT STUDY ON DRUGS

To evaluate the usefulness of Dexmedetomidine during Carotid Endarterectomy.

Primary endpoint: minor and major adverse events.

Secondary endpoint: satisfaction of the Patient, the Anesthetist and the Surgeon (4=very satisfied, 3=satisfied, 2=not very satisfied, 1=not satisfied), possible reduction in clamping times, number of times the Surgeon needs to administer local anesthesia (Lidocaine 0.5%).

METHODS

Patient selection

All patients admitted to the Vascular Surgery Unit who are candidates for Carotid Endarterectomy will be considered eligible for the study.

Patients with the following will be excluded:

-Severe hepatic insufficiency or severe hypoproteinemia (increased percentage of free dexdor)

-Age <18 years

-Baseline heart rate < 50 bpm

-BAV II or III without PMK

-Reduced ANS activity

-Suspected or confirmed malignant hyperthermia

-Psychiatric disorders

-Breastfeeding

-Suspected or confirmed pregnancy

-Urgent interventions

-Inability to express valid consent to the procedure

Anamnestic data, surgical time, clamping time, percentage of shunt and conversion to general anesthesia, intraprocedural complications and in the 4 hours postoperatively (e.g. severe bradycardia <40 bpm, SpO2 <85%, alterations in depth of consciousness) will be noted.

Patients will be divided into two groups in relation to the type of sedation expected:

Group 1 - standard sedation with Fentanyl 1y/kg + Midazolam 0.03 mg/kg

Group 2 - sedation with Dexmedetomidine 1 y/kg/min for 10 minutes and then 0.3-0-5 y/kg/min until reaching a Richmond Agitation-Sedation Scale (RASS)=-1/-2. Both techniques are used in common clinical practice.

The administration of drugs will always be carried out by the same Anesthetist.

Patient monitoring

All patients, after informed consent, will undergo Carotid Endarterectomy under continuous monitoring of cardiac, respiratory and neurological activities. Cardiac activity will be monitored by ECG while respiratory activity will be monitored by monitoring the respiratory acts with direct observation of the chest and evaluation of O2 saturation (SaO2) by pulse oximetry. A reduction in SaO2 <90% will be defined as a mild desaturation episode and <85% as a severe one, and they will be rebalanced ad hoc. Diastolic, systolic and mean blood pressure will be evaluated beat-by-beat via arterial catheter during the operation and in the Recovery Room. The heart rate will be assessed with

a monitor and will be defined as mild bradycardia <50 bpm and severe <40 bpm, injection therapy with atropine (0.1 mg/kg) or other will be implemented if deemed necessary. At the end of the intervention, the patient will be monitored in the following 4 hours, and discharged according to the Aldrete's criteria, reporting the times of discharge from the recovery room.

STATISTICAL ANALYSIS

Evaluation of data and results

Since this is a preliminary study, it is not possible to perform a statistical calculation of the sample size due to the lack of statistics suitable for the purpose. It is planned to enroll 60 patients treated in common clinical practice, 30 treated with Fentanyl + Midazolam, and 30 with Dexmedetomidine. The two groups of patients will be compared based on the parameters evaluated. The statistical analysis will be performed using the chi-square or Fisher test for the comparison of proportions, and the Student t test for the comparison of means ± SD.

BIBLIOGRAPHY

1 Kesisoglou I, Papavramidis T, Michalopoulos N, Ioannidis K, Trikoupi A, Sapalidis K, et al. Superficial selective cervical plexus block following total thyroidectomy: a randomized trial. Head Neck 2010; 32: 984-8

2 Tobias JD. Cervical plexus block in adolescents. J Clin Anesth 1999; 11: 606-8

3 Perisanidis C, Saranteas T, Kostopanagiotou G. Ultrasound-guided combined intermediate and deep cervical plexus nerve block for regional anaesthesia in oral and maxillofacial surgery. Dentomaxillofac Radiol 2013; 42: 29945724

4 Suresh S, Barcelona SL, Young NM, Seligman I, Heffner CL, Coté CJ. Postoperative pain relief in children undergoing tympanomastoid surgery: is a regional block better than opioids? Anesth Analg 2002; 94: 859-62

5 Mariappan R, Mehta J, Massicotte E, Nagappa M, Manninen P, Venkatraghavan L. Effect of superficial cervical plexus block on postoperative quality of recovery after anterior cervical discectomy and fusion: a randomized controlled trial. Can J Anaesth 2015; 62: 883- 90

6 Hardy D. Relief of pain in acute herpes zoster by nerve blocks and possible prevention of post-herpetic neuralgia. Can J Anaesth 2005; 52: 186-90

7 Shin HY, Kim DS, Kim SS. Superficial cervical plexus block for management of herpes zoster neuralgia in the C3 dermatome: a case report.J Med Case Rep 2014; 8: 59

8 Ramachandran SK, Picton P, Shanks A, Dorje P, Pandit JJ. Comparison of intermediate vs subcutaneous cervical plexus block for carotid endarterectomy. Br J Anaesth 2011; 107: 157-63

9 Martusevicius R, Swiatek F, Joergensen LG, Nielsen HB. Ultrasound-guided locoregional anaesthesia for carotid endarterectomy: a prospective observational study. Eur J Vasc Endovasc Surg 2012; 44: 27-30

10 Stoneham MD, Doyle AR, Knighton JD, Dorje P, Stanley JC. Prospective, randomized comparison of deep or superficial

cervical plexus block for carotid endarterectomy surgery. Anesthesiology 1998; 89: 907-12

11 Rössel T, Kersting S, Heller AR, Koch T. Combination of high-resolution ultrasound-guided perivascular regional anesthesia of the internal carotid artery and intermediate cervical plexus block for carotid surgery. Ultrasound Med Biol 2013; 39: 981-6

12 Pandit JJ, Satya-Krishna R, Gration P. Superficial or deep cervical plexus block for carotid endarterectomy: a systematic review of complications. Br J Anaesth 2007; 99: 159-69

13 Cervical plexus block. Kim JS , Ko JS, Bang S, Kim H, Lee SY. Korean J Anesthesiol 2018 August 71(4): 274-288

14 North Am Symptomatic Carotid Endarterectomy Trial Collaborative (NASCET). Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. NEJM 1991;325:445–53.

15 Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. JAMA 1995;273:1421–8

16 Halliday A, Mansfield A, Marro J, Peto C, Peto R et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet 2004;363:1491–502

17 Hobson RW II, Weiss DG, Fields WS, Goldstone J, Moore WS et al. Group TVACS. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. NEJM 1993;328:221–7

18 Ferguson GG, Eliasziw M, Barr HW, Clagett GP, Barnes RW et al. The North Am Symptomatic Carotid Endarterectomy Trial: surgical results in 1415 patients. Stroke 1999;30:1751–8

19 GALA Trial Collaborative Group, Lewis SC, Warlow CP, Bodenham AR, et al. General anaesthesia versus local anaesthesia for carotid surgery (GALA): a multicentre, randomised controlled trial. Lancet 2008; 372: 2132–42

20 Gurer O, Yapici F, Yapici N, Ozler A, Isßik O. Comparison between local and general anesthesia for carotid endarterectomy: early and late results. Vascular and Endovascular Surgery 2012; 46: 131–8

21 Benington S, Pichel AC. Anaesthesia for carotid endarterectomy. Current Anaesthesia and Critical Care 2008; 19: 138–49

22 Zdrehuş C. Anaesthesia for carotid endarterectomy – general or loco-regional? Romanian Journal of Anaesthesia and Intensive Care 2015 Vol 22 No 1, 17-24

23 Heyer EJ, Gold MI, Kirby EW, Zurica J, Mitchell E et al. A study of cognitive dysfunction in patients having carotid endarterectomy performed with regional anesthesia. Anesth Analg 2008 Aug;107(2):636-42.

24 Hakl M, Michalek P, Sevcik P, Pavlikova J, Stern M. Regional anaesthesia for carotid endarterectomy: an audit over 10 years. British Journal of Anaesthesia 2007; 99: 415–20

25 Pandit JJ, Satya-Krishna R, Gration P. Superficial or deep cervical plexus block for carotid endarterectomy: a systematic review of complications. British Journal of Anaesthesia 2007;99: 159–69

26 Calderon AL, Zetlaoui P, Benatir F, Davidson J, Desebbe O et al. Ultrasound-guided intermediate cervical plexus block for carotid endarterectomy using a new anterior approach:a two-centre prospective observational study. Anaesthesia 2015 Apr;70(4):445-51

27 Scimia P, Giordano C, Basso Ricci E, Petrucci E, Fusco P. The ultrasound-guided C2-C4 compartment block combined to dexmedetomidine sedation:an ideal approach for carotid endarterectomy in awake patients. Min Anaest 2018 Oct;84(10):1226-7

28 Nacif-Coelho C, Correa-Sales C, Chang LL, Maze M. Perturbation of ion channel conductance alters the hypnotic response to the alpha 2-adrenergic agonist dexmedetomidine in the locus coeruleus of the rat. Anesthesiology 1994; 81: 1527-34.

29 Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. Anesth Analg. 2000;90:699–705

30 Rahimzadeh P, Faiz SHR, Imani F, Derakhshan P, Amniati S. Comparative addition of dexmedetomidine and fentanyl to intrathecal bupivacaine in orthopedic procedure in lower limbs. BMC Anesthe- siol. 2018;18(1):62

31 Dyck JB, Maze M, Haack C, Vuorilehto L, Shafer SL. The pharmacokinetics and hemodynamic effects of intravenous and intramuscular dexmedetomidine hydrochloride in adult human volunteers. Anesthesiology. 1993;78:813–20.

32 Gurbet A, Basagan-Mogol E, Turker G, Ugun F, Kaya FN, Ozcan B, et al. Intraoperative infusion of dexmedetomidine reduces perioperative analgesic requirements. Can J Anaesth. 2006;53:646–52.

33 Tufanogullari B, White PF, Peixoto MP, Kianpour D, Lacour T, Griffin J, et al. Dexmedetomidine infusion during laparoscopic bariatric surgery: The effect on recovery outcome variables. Anesth Analg. 2008;106:1741–8.

34 Jaakola ML, Ali-Melkkilä T, Kanto J, Kallio A, Scheinin H, Scheinin M, et al. Dexmedetomidine reduces intraocular pressure, intubation responses and anaesthetic requirements in patients undergoing ophthalmic surgery. Br J Anaesth. 1992;68:570–5.

35 Ghali A, Mahfouz AK, Ihanamäki T, El Btarny AM. Dexmedetomidine versus propofol for sedation in patients undergoing vitreoretinal surgery under sub-tenon's anesthesia. Saudi J Anaesth. 2011;5:36–41

36 Aho M, Erkola O, Kallio A, Scheinin H, Korttila K. Dexmedetomidine infusion for maintenance of anesthesia in patients undergoing abdominal hysterectomy. Anesth Analg. 1992;75:940–6

37 Aantaa R, Kanto J, Scheinin M, Kallio A, Scheinin H. Dexmedetomidine, an alpha 2-adrenoceptor agonist, reduces anesthetic requirements for patients undergoing minor gynecologic surgery. Anesthesiology. 1990;73:230–5

38 Bergese SD, Patrick Bender S, McSweeney TD, Fernandez S, Dzwonczyk R, Sage K, et al. A comparative study of dexmedetomidine with midazolam and midazolam alone for sedation during elective awake fiberoptic intubation. J Clin Anesth. 2010;22:35–40

39 Mathru M, Esch O, Lang J, Herbert ME, Chaljub G, Goodacre B, vanSonnenberg E. Magnetic resonance imaging of the upper airway. Effects of propofol anesthesia and nasal continous positive airway pressure in humans. Anesthesiology. 1996;84(2):273-9

40 Sundman E, Witt H, Sandin R, Kuylenstierna R, Bdoen K, Edberg O, Ericsson LI. Pharingeal function and airway protezione during subhypnotic concentrations of propofol, isoflurane, and sevoflurane: volunteers esaminate by pharyngeal videoradiography and simultaneous manometry. Anesthesiology. 2001;95(5):1125-32

41 Mahmoud M, Jung D, Salisbury S, McAuliffe J, Gunter J, Patio M, Donnelly LF, Fleck R. Effect of increasing depth of dexmedetomidine and propofol anesthesia on upper airway morphology in children and adolescents with obstructive sleep apnea.J Clin Anesth. 2013;25(7):529–41

42 Shin HJ et al. Comparison of upper airway potency in patients with mild obstructive sleep apnea during dexmedetomidine or propofol sedation: a prospective, randomized, controlled trial. BMC Anesthesiology. 2018;18:120

43 Wu W, Chen Q, Zhang LC, Chen WH. Dexmedetomidine versus mida- zolam for sedation in upper gastrointestinal endoscopy.J Int Med Res. 2014;42(2):516–22

44 Jalowiecki P, Rudner R, Gonciarz M, Kawecki P, Petelenz M, Dziurdzik P. Sole use of dexmedetomidine has limited utility for conscious sedation during outpatient colonoscopy. Anesthesiology. 2005;103(2):269– 73

45 Dere K, Sucullu I, Budak ET, Yeyen S, Filiz AI, Ozkan S, et al. A comparison of dexmedetomidine versus midazolam for sedation, pain and hemodynamic control, during colonoscopy under conscious sedation. Eur J Anaesthesiol. 2010;27(7):648–52

46 Sidorowicz M, Owczuk R, Kwiecinska B, Wujtewicz MA et al. Dexmedetomidine sedation for carotid endarterectomy. Anestezjol Intens Ter Apr-Jun 2009;41(2):78.83

47 Bekker AY, Basile J, Gold M, Riles T, Adelman M, Cuff G et al. Dexmedetomidine for awake carotid endarterectomy: efficacy, hemodynamic profile, and side effects.J Neurosurg Anesthesiol 2004 Apr;16(2):126-35

48 McCutcheon CA, Orme RM, Scott DA, Davies MJ, McGlade DP. A comparison of dexmedetomidine versus conventional therapy for sedation and hemodynamic control during carotid endarterectomy performed under regional anesthesia. Anesth Analg. 2006 Mar;102(3):668-75

49 Do W, Cho AR, Kim EJ, Kim HJ, Kim E, Lee HJ. Ultrasound-guided superficial cervical plexus block under dexmedetomidine sedation versus general anesthesia for carotid endarterectomy: a retrospective pilot study. Yeungnam Univ J Med 2018;35(1):45-53