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Target-controlled infusion during MitraClip procedures in deep-sedation with spontaneous breathing

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Abstract. – OBJECTIVE: Percutaneous mitral valve repair with the MitraClip system is an alternative procedure for high-risk patients not suitable for conventional surgery. The MitraClip can be safely performed under general anesthesia (GA) or deep sedation (DS) with spontaneous breathing using a combination of propofol and remifentanil. This study aimed to evaluate the benefits of target-controlled infusion (TCI) of remifentanil and administration of propofol during DS compared with manual administration of total intravenous anesthesia (TIVA) medication during GA in patients undergoing MitraClip. We assessed the impact of these procedures in terms of remifentanil dose, hemodynamic profile, adverse events, and days of hospital stay after the process.

PATIENTS AND METHODS: From March 2013 to June 2015 (mean age 73.5 ± 9,54), patients underwent transcatheter MitraClip repair, 27 received DS via TCI and 27 GA with TIVA.

RESULTS: Acute procedural success was 100%. DS-TCI group, in addition to a significant reduction of remifentanil dose administrated (249 μg *vs.* 2865, $p < 0.01$), resulted in a decrease in vasopressor drugs requirement for hemodynamic adjustments (29.6% *vs.* 63%, $p = 0.03$) during the procedure and a reduction of hypotension ($p = 0.08$). The duration of postoperative hospitalization did not differ between the two groups (5.4 days vs. 5.8 days, $p = 0.4$).

CONCLUSIONS: Administration of remifentanil by TCI for DS in spontaneously breathing patients offers stable anesthesia conditions, with a lower amount of drugs, higher hemodynamic stability, and decreased side effects.

Key Words:
MitraClip, TIVA, TCI, Mitral regurgitation, TEER.

Introduction

Transcatheter Edge-to-Edge Repair (TEER) with MitraClip implantation is a minimal-invasive treatment recommended in selected symptomatic patients with severe secondary mitral regurgitation (MR) despite optimal medical therapy, not eligible for surgery and fulfilling anatomical and functional criteria that suggest an increased chance of responding to treatment[1]. The MitraClip System (Abbott Vascular, Abbott Park, IL, USA) is a dedicated device for percutaneous repair of MR, which reproduces Alfieri's edge-to-edge technique[2]. The MitraClip system received initial CE-Mark approval in Europe in 2008 and was approved by the Food and Drug Administration (FDA) in 2013[3]. It has been associated with a reduction in the severity of MR and left ventricular volume, as well as an improvement in functional status, a lower rate of hospitalisation for heart failure, lower all-cause mortality, and a better quality of life in high-risk patients who are not suitable for conventional heart surgery[4-8]. The standard anesthesiologic management was general anesthesia (GA), but TEER can also be performed efficaciously and safely in Deep-Sedation (DS) with spontaneous breathing[9-11]. Anesthesiologic management is frequently achieved with the combination of propofol-remifentanil by TIVA (Total Intravenous Anesthesia) during GA, which allows for obtaining adequate amnesia, and immobility, and analgesia. Still, it increases the risks of post-procedural respiratory depression, hypotension, bradycardia, and musculoskeletal stiff-

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ness[12]. The incidence of both drugs' side effects could be reduced by the Target Controlled Infusion (TCI) technique, a computer-assisted modality of intravenous drug administration that achieves and maintains targeted blood or effect-site concentration, according to the pharmacokinetic model and algorithm of Minto for remifentanil[13].

The main advantages of the TCI method are avoiding drug overdose and reducing drug-related side effects that are common with total intravenous anesthesia (TIVA) infusion[11-13]. The administration of a reduced dose of the drug via TCI could be associated with better hemodynamic stability during the procedure, a lower incidence of side effects, and a shorter duration of postoperative hospital stay. This is a preliminary study that evaluated a small patient population and compared TCI administration of remifentanil in DS with spontaneous breathing to GA with TIVA for propofol and remifentanil infusion in patients undergoing TEER with MitraClip[10,11].

Patients and Methods

Study Population

This retrospective observational study includes 54 consecutive patients who underwent TEER with MitraClip System in our Institution from March 2013 to June 2015. Patients were considered at high risk for conventional mitral valve surgery, after evaluation by an interdisciplinary "heart team" (consisting of clinical cardiologist, interventional cardiologist, cardiac surgeon, and cardiac anesthesiologist), according to clinical history and examination, chest X-ray, spirometry, coronary angiography, transthoracic echocardiogram (TTE) and transesophageal echocardiography (TEE). The European System for Cardiac Operative Risk Evaluation (EuroSCORE) was used for risk stratification in TEER candidates. Inclusion criteria for MitraClip repair were severe MR, patients unsuitable to cardiac surgery, anatomical feasibility (mitral valve area > 4 cm^2, absence of annulus and leaflet calcifications, anatomy suitable for correct positioning of the clip or adequate reduction of valvular regurgitation). Exclusion criteria were: acute myocardial infarction in the last twelve weeks; active/history of endocarditis, rheumatic valve disease; septic shock; pulmonary consolidations; fever and increased inflammatory markers; patients with oro-tracheal intubation (OTI) or tracheostomy and impaired respiratory function with poor clinical conditions and/or septic shock, hypertrophic cardiomyopathy and systolic anterior motion of the anterior leaflet; ictus or TIA in the last six months; contraindications to transesophageal echocardiography. Patients were divided into two groups: DS group (27 patients enrolled between February 2014 and June 2015), in which remifentanil was administrated via TCI and GA group, where it was given using TIVA (27 patients, treated between March 2013 and January 2014). According to our institutional protocol, patients with left ventricle ejection fraction (LVEF) ≤ 30% received inotropic pharmacological treatment with Levosimendan (continuous infusion of 0.1 μg/kg/min, from the beginning of the procedure and throughout the intraoperative and postoperative period). Informed written consent of each patient and approval of the Ethics Committee were obtained.

Anesthesiologic Management

Anesthesiologic management for TEER procedures consisted of Deep-Sedation (DS) with spontaneous breathing, a state of hypnosis, amnesia, and analgesia without respiratory depression. The remifentanil infusion was immediately started upon the patient's arrival in the catheterization room. All patients were equipped with nasal goggles to administer 4 lt/min of Oxygen during the procedure. We recorded: oxygen saturation (SpO_2), partial pressure of oxygen (FiO_2%), non-invasive systemic blood pressure (NIBP), heart rate (HR), number of breaths/minute, and bi-spectral index (BIS) monitoring, end-expiratory CO_2 partial pressure ($EtCO_2$) through an adequately calibrated device called *Microstream Smart CapnoLine Guardian* O_2. The DS in spontaneous breathing was obtained with a single bolus dose of midazolam (0.06 mg/kg) and a single bolus dose of propofol (0.5 mg/kg); 1% lidocaine was applied subcutaneously into arterial and venous access sites (maximum doses 4 mg/kg). Anesthesia was maintained by continuous infusion of remifentanil. In the DS-TCI group, the drug was administrated using the Minto Pharmacokinetic Model; the initial effect-site concentration was 1-1.5 ng/ml[13]. In the GA group, TIVA infused remifentanil, beginning with the infusion of a dose ranging from 0.1 μg/kg/min to 0.15 μg/kg/min. The amount to be infused was titrated in increments of 0.025 μg/kg/min to reach the desired level of analgesia the propofol dosage for maintenance of a GA with TIVA is 6-12 mg/kg/h. Our institutional protocol for elective OTI

during GA is propofol 2-2.5 mg/kg iv; fentanest 3 mcg/kg iv or sufentanil 0.3 mcg/kg iv; rocuronium 0.6 mg/kg iv (for OTI in rapid succession, 1 mg/kg iv, after 3 min preoxygenation)

Our goals were to maintain:

- BIS values between 50 and 60 throughout the intraoperative period to achieve a state of adequate anesthesia deep enough to achieve analgesia and amnesia and avoid intraoperative awakening, but shallow enough to maintain intact airway reflexes and spontaneous breathing.

- Blood pressure above 120/80 mmHg. Hypotension (systolic arterial pressure < 90 mmHg or a drop > 30% from baseline lasting longer than 1 minute) was treated by infusion of norepinephrine (0.05 - 0.1 μg/kg/min).

In case of desaturation (SpO_2 < 90%) or apnea > 20-sec ventilation, patients were assisted by a facial mask until an adequate respiratory drive was recovered. In procedural complications, OTI using rocuronium (1 mg/kg) and 2% vol severance were achieved.

When $EtCO_2$ increased from 30% to 50% of baseline and hypotension occurred, the patient was supported with a face mask. The drug dose administered with the computer-controlled TCI pump could be titrated and adjusted. At the end of the procedures, patients were awakened in the cath lab and transferred to the cardiologic care unit (CCU).

Statistical Analysis

The primary cumulative endpoint was comparing TCI in DS *vs.* TIVA in GA patients according to duration, remifentanil dose, intraprocedural administration of vasopressors drugs and duration of postoperative hospitalization. All data were tested for normal distribution using the Shapiro-Wilk normality test. Descriptive statistic was used to summarize data. Continuous variables were expressed as mean ± standard deviation and categorical variables were presented as frequencies and percentages. Differences between groups were compared using Student's two-tailed *t*-test and the Chi-square test. *p*-values of less than 0.05 were regarded as statistically significant. Statistical analyses were performed using the Statistical Package for Social Sciences, version 26 (SPSS Corp., Armonk, NY, USA).

Results

The overall mean age of our study population was 73.5 ± 9 years and 67% were males. LogEuroSCORE and EuroSCORE II were 18.5± 14.4% and 8.5 ± 7.5%, respectively. Demographics and clinical data are reported in Table I. Acute procedural success was 100%. In the GA-TIVA group, the mean age was 72.3 ± 10 years [range 38-88], similarly to the DS-TCI group, in which it was 74.8 ± 7.4 years [range 58-87] (p = 0.3). No significant differences were present in gender distribution (males 81% *vs.* 70%, p = 0.5) and patients BMI (25.6 ± 4.3 *vs.* 24.9 ± 3.7 kg/m^2, p = 0.5), between the two groups. Chronic obstructive pulmonary disease was present in 55.5% of GA-TIVA patients and 33.3% of DS-TCI patients (p = 0.2) and chronic renal failure in 44% of GA-TIVA patients and 48% of DS-TCI patients (p = 1). In GA-TIVA and DS-TCI groups, 6 patients (22%) and one patient (4%) underwent coronary artery bypass grafting respectively (p = 0.1), while 1 patient in both groups (p = 0.5) underwent previous surgical mitral valve annuloplasty. LogEuroSCORE and EuroSCORE II were 17.9 ± 15.1% and 8.9 ± 9.5%, respectively for TIVA-group, while they were 19.3 ± 13.3% and 8.3± 4.1% for TCI-group (p = 0.7 for LogEuroSCORE and p = 0.8 for EuroSCORE II). Mitral regurgitation was severe (4+) in 33% of the GA-TIVA group and 51.9% of the DS-TCI group (p = 0.3), moderate-to-severe (3+) in 63% of the GA-TIVA group and 48.1% of DS-TCI group (p = 0.4), moderate (2+) in 3.7% of GA-TIVA group and nobody of DS-TCI group (p = 1). The LVEF was 35.8 ± 11.3% for the GA-TIVA group and 32.2 ± 9.5% for the DS-TCI group (p = 0.2). NYHA functional class II-IV was present in 93% of GA-TIVA patients and 100% DS-TCI patients (p = 0.5) (Table I). Perioperative data are summarized in Table II. No statistically significant difference was reported between TIVA and TCI groups (79.2 ± 30.9 *vs.* 68.3 ± 21.3 minutes, p = 0.13). The dose of remifentanil used for a single patient was 2685.7 ± 1368.6 μg in TIVA-group and significantly less in TCI-group with 248.9 ± 99.6 μg (p < 0.01) (Figure 1A). Levosimendan infusion was used in 48% of both groups of patients (p = 0.8), while norepinephrine infusion was necessary for 63% of the GA-TIVA group and 29.6% of the DS-TCI group (p = 0.03) (Figure 1B). The mean duration of the postoperative stay was 5.8 ± 1.5 days (3.7 ± 1.4 in ICU) in the GA-TIVA group and 5.4 ± 2.2 days (3.6 ±1.8 in ICU) in DS-TCI-group, (p = 0.4 for total postoperative stay, p = 0.8 for postoperative CCU stay) (Figure 1C). No significant differences between groups were found regarding the values of systolic and diastolic blood pressure in the pre-operative and postoperative periods. The change of anesthesiologic manage-

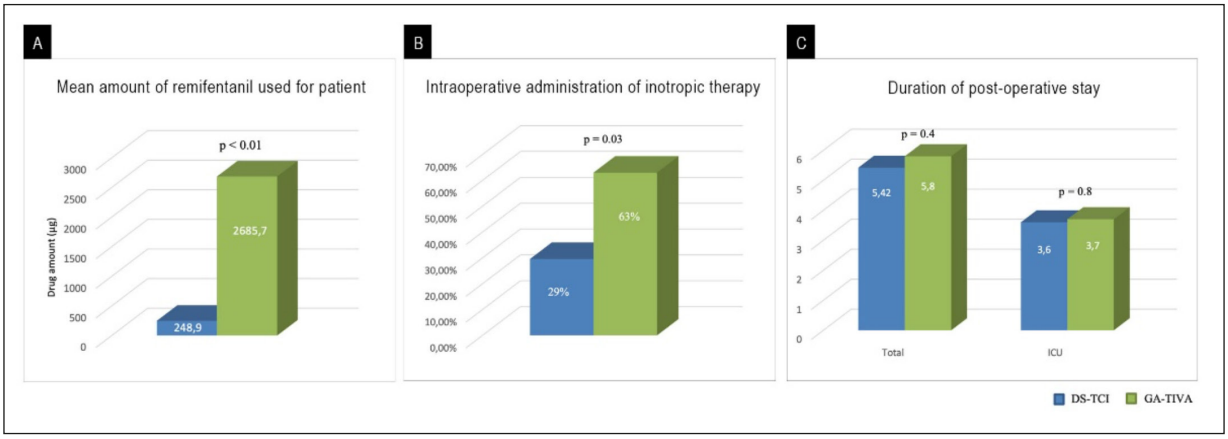

Figure 1. **A**, Mean amount of remifentanil (µg) used for a single patient. **B**, Intraoperative administration of inotropic therapy. **C**, Duration of postoperative stay. DS-TCI: Deep Sedation- Target-Controlled Infusion; GA: General Anesthesia; TIVA = total intravenous anesthesia.

ment from DS to GA with OTI was necessary for only two patients (7.4%). Finally, the data relating to the mean values of plasmatic concentration and effect-site concentration at the end of the procedure show the possibility of obtaining adequate anesthesia and analgesia with a poor remifentanil concentration.

Discussion

Our study has compared TCI in DS *vs.* TIVA in GA for remifentanil infusion in patients undergoing TEER with MitraClip, evaluating the following parameters: duration of anesthesia, remifentanil dose, intraprocedural administration of inotropic and vasopressor drugs, duration of postoperative hospitalization. Patients' demographic and clinical data were similar between groups, demonstrating that the study involved a homogeneous population. We demonstrated the advantages of remifentanil administration via TCI regarding the dose of remifentanil administered. The mean dose of remifentanil for each patient resulted significantly lower in TCI-group, with a mean amount expressed in µg 10 times lower than the TIVA group ($p < 0.01$). The significant dose reduction seems associated with a trend toward better hemodynamic stability during the MitraClip procedure because of the less frequent utilization of norepinephrine infusion in the TCI group ($p = 0.02$).

Nowadays, several percutaneous approaches for the treatment of mitral valve regurgitation are proposed[14-18]. TEER with MitraClip System is a consolidated option for patients with mitral regurgitation deemed inoperable or at high risk for conventional surgery. Commonly, the procedure is performed under GA, but different anesthesiologic management has been described, and the sedation with the combined use of propofol-remifentanil[4-6,12,13]. Remifentanil is an opioid 250 times more potent than morphine with a rapid onset and offsets and with a quick clearance (2.5-3 L/min); this drug can be used safely in patients with renal and hepatic failure and reduced cardiac output because it doesn't modify intraoperative hemodynamic stability.

Remifentanil is used in cardiac surgery and is associated with adequate anesthesia and analgesia and earlier weaning. Moreover, it is successfully used for minimally invasive cardiologic techniques and improves the comfort in transesophageal echocardiography[19]. Performing the procedure in DS with spontaneous breathing avoids the hemodynamic impact of positive pressure ventilation, which causes a reduction of diastolic ventricular filling, already compromised in patients with severe mitral regurgitation. Previous studies in patients undergoing OTI have already shown that remifentanil administration via TCI compared with manual infusion is associated with higher hemodynamic stability, with more minor hypotensive episodes during the induction of anesthesia and fewer episodes of tachycardia[20]; moreover, the administration via TCI reduces remifentanil requirements, and it allows better control of the depth of anesthesia and a more rap-

id awake in comparison with the manual infusion. To the best of our knowledge, this is the first report about the use of TCI DS with spontaneous breathing for TEER procedures. This result could have a clinical impact, especially for elderly and frail patients, who have a higher pharmacodynamics sensibility to opioids and who represent the typical patients treated with TEER. A final consideration concerns an economic evaluation and the optimization of resources. Remifentanil is an expensive drug; the use of TCI instead of TIVA leads to a net saving of the drug dose and lower costs associated with the procedure.

Study Limitation

The main limitation of this study is its retrospective nature and single-site data collection and small sample size, even if no other studies have been currently published on this focus. In consideration of the small sample size and the study design, we cannot make meaningful statistical conclusions and consider it a preliminary and hypothesis-generating study. Additionally, the sample size of the research and its single-center nature may not reflect the experience of other centers. Our results must be confirmed in larger prospective or randomized studies.

Conclusions

Our study has compared the TCI technique with manual infusion for the administration of remifentanil in TEER. The administration via

Table I. Percentage of medical and non-medical students correctly identifying statements regarding hydration.

	GA-TIVA (27)	DS-TCI (27)	p
Age, years ± SD	72.3 ± 10	74.8 ± 7.4	0.3
Weight, kg ± SD	69.7 ± 14.8	68.8 ± 10.8	0.8
Height, cm ± SD	164.6 ± 10	166.2 ± 7.7	0.5
Male, n (%)	22 (81)	19 (70)	0.5
BMI, kg/m^2 ± SD	25.6 ± 4.3	24.9 ± 3.7	0.5
COPD, n (%)	15 (55.5%)	9 (33.3%)	0.2
Diabetes mellitus, n (%)	8 (29.6%)	9 (33.3%)	1
Hypertension, n (%)	22 (81.5%)	19 (70.4%)	0.5
Dyslipidemia, n (%)	18 (81.8%)	12 (44.4%)	0.2
Ex-smoker, n (%)	13 (48.1%)	9 (33.3%)	0.4
AF, n (%)	14 (51.2%)	13 (48.1%)	1
Creatinine, mg/dl ± SD	1.51 ± 0.56	1.64 ± 0.57	0.4
CRF, n (%)	44%	48%	1
Previous PTCA	12 (44.4%)	10 (37%)	0.8
Previous CABG	6 (22.2%)	1 (3.7%)	0.1
Previous mitral valve annuloplasty	1 (3.7%)	1 (3.7%)	0.5
Previous pace-maker implantation	11 (40.7%)	5 (18.5%)	0.1
LogEuroSCORE ± SD	17.9 ± 15.1	17.9 ± 15.1	0.7
EuroSCORE II ± SD	8.9 ± 9.5	8.9 ± 9.5	0.8
NYHA (%)			
NYHA (%)			
I	7.4% (2)	7.4% (2)	0.5
II	33.3% (9)	33.3% (9)	0.003
III	55.6% (15)	55.6% (15)	0.2
IV	3.7% (1)	3.7% (1)	0.1
EF (%)	35.8 ± 11.3	35.8 ± 11.3	0.2
MR severity (+)			
2+	1 (3.7%)	1 (3.7%)	1
3+	17 (63%)	17 (63%)	0.4
4+	9 (33.3%)	9 (33.3%)	0.3
Arterial pressure, (mmHg ± SD)			
SAP	117.6 ± 20.4	117.6 ± 20.4	0.6
DAP	62.3 ± 6.4	62.3 ± 6.4	0.5

Data are expressed as mean standard deviation or percentages. TIVA = total intravenous anesthesia; TCI = target-controlled infusion; BMI: body mass index; COPD: chronic obstructive pulmonary disease; AF: atrial fibrillation; AMI: acute myocardial infarction; CRF: chronic renal failure; PTCA: percutaneous transluminal coronary angioplasty; CABG: coronary artery bypass grafting; EF: ejection fraction; MR: mitral regurgitation; SAP: systolic arterial pressure; DAP: diastolic arterial pressure.

Table II. Peri-operative data. Data are expressed as mean ± standard deviation or percentages.

	TIVA (27)	TCI (27)	*p*
Intra-operative data			
Duration of anesthesia, min ± SD	79.2 ± 30.9	68.3 ± 21.3	0.13
Number of clips implanted			
1	10 (37%)	14 (51.8%)	0.4
2	16 (59.3%)	13 (48.1%)	0.3
3	1 (3.7%)	0 (0%)	1
Patients received Levosimendan infusion, n (%)	13 (48%)	13 (48%)	1
Patients received norepinephrine infusion, n (%)	17 (63%)	8 (29.6%)	0.03
Shift in GA with OTI, n (%)	1 (3.7%)	2 (7.4%)	1
Dose Remifentanil/patient, µg ± SD	2685.7 ± 1368.6	248.9 ± 99.6	< 0.01
Post-operative data			
Arterial pressure, mmHg ± SD			
SAP	126.5 ± 21.3	135.9 ± 18.3	0.08
DAP	66.5 ± 6.7	71 ± 13.1	0.1
DAP	62.3 ± 6.4	62.3 ± 6.4	0.5

TCI = target-controlled infusion; TIVA = total intravenous anesthesia; SAP: systolic arterial pressure; DAP: diastolic arterial pressure; GA: general anesthesia; OTI: oro-tracheal intubation. ICU: intensive unit care.

TCI was associated with lower remifentanil requirements. We also demonstrate a lower necessity of intraoperative vasopressor therapy. Even if this study was monocentric and involved a small number of patients, we have obtained promising results that a more comprehensive randomized study should confirm.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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Authors' Contributions
P. De Vico: Conceptualization and Writing-Original Draft Preparation, V. Cammalleri: Investigation, F.R. Prandi, D. Lecis and G. Idone: Formal Analysis, G. Massaro: Validation, M. Marchei and A. Di Landro: Data Curation, A. Zingaro: Formal Analysis, M. Macrini: Methodology, M. Di Luozzo: Validation, G.P. Ussia: Methodology, F. Romeo: Data Curation and Supervision, M. Dauri: Funding Acquisition, S. Muscoli: Project Administration and Writing - Review & Editing.

Ethics Approval
The study was conducted in accordance with the Declaration of Helsinki and approved by the local Ethics Committee of Policlinico Tor Vergata (approval code 49/21).

Informed Consent
Informed consent was obtained from all subjects involved in the study.

Data Availability Statement
Data files are available upon request.

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