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Review

What is the place of clonidine in anesthesia? Systematic review and meta-analyses of randomized controlled trials

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ABSTRACT

Study objective: A place for clonidine has been suggested for many indications in perioperative medicine. The aim of this systematic review and these meta-analyses is to systematically, and quantitatively, evaluate these potential indications of clonidine.
Design, setting, patients and interventions: We selected and analyzed (qualitatively and, when possible, quantitatively) the available literature published on PubMed/Medline and on the Cochrane database. Inclusion criteria included: human randomized controlled trials involving adults who received perioperative systemic (oral, intramuscular, transdermal and intravenous) clonidine for every type of surgery.
Measurements and main results: We identified 775 trials and thereafter excluded 718 and analyzed 57 trials concerning, in total, 14,790 patients of whom 7408 received clonidine and 6836 received placebo. Most important results shows that, in qualitative and quantitative analyses, clonidine vs placebo reduces analgesics consumption in, respectively, (159 vs 154 patients: 24%, 95%CI[16%–32%]; $p < 0.001$), reduces nausea and vomiting (risk ratio, in 180 vs 181 patients: 0.35, 95%CI[0.25–0.51]; $p < 0.001$), improves hemodynamic stability (reduction of HR: 14.9 bpm, 95%CI[10.4–19.5]; $p < 0.001$; reduction of the MAP: 12.5 mm Hg, 95%CI[7.14–17.86]; $p < 0.001$); 1 min after tracheal intubation, in 67 vs 68 patients), prevents postoperative shivering (risk ratio, in 140 vs 140 patients: 0.17, 95%CI[0.10–0.29]; $p < 0.001$). On the other hand, clonidine does not have any influence on renal and cardiac outcomes (adverse events rates, in 5873 vs 5533 patients: 0.00, 95%CI[−0.10–0.11]; $p = 0.96$) and does not prolong awakening time.
Conclusions: In conclusion, these systematic review and meta-analyses of 57 trials confirm that clonidine improves pain control, reduces PONV, improves hemodynamic and sympathetic stability, with no adverse consequences on renal function or awakening time, but does not influence cardiac outcome in the general population, after non-cardiac surgery. Nevertheless, given the high heterogeneity between the studies, this does not exclude different results in patient subgroups or specific procedures.

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1. Introduction

After the results of the PeriOperative Ischemic Evaluation-2 (POISE-2) study, a large multicentric study, suggesting that clonidine does not improve the cardiac outcome of the patients in non-cardiac surgery [1], it appears important to evaluate if clonidine has still a place in anesthesia. Indeed, these negative results may introduce doubts concerning the added value of clonidine in the perioperative period. A definitive evidence in other indications than prevention of myocardial infarction may help the anesthesiologist to have a clear vision about the place of clonidine.

Undergoing anesthesia and surgery is associated with specific risks and complications before, during and after the procedure. To provide patient comfort and safety is the objective of the anesthesiologist.

Clonidine is a centrally acting imidazolin α2-adrenergic agonist, analog of norepinephrine. The pre-synaptic stimulation of α2-receptors is coupled via G-protein to several effectors including inhibition of adenylate cyclase and effects on potassium and calcium channels [2] that finally restricts the release of norepinephrine in the central nervous system (in the nucleus tractus solitaries and nucleus reticularis lateralis region of rostroventro-lateral medulla). Clonidine was synthesized for the first time in 1962 in Germany. At the beginning it was commercialized as antihypertensive drug and many years later his use in anesthesia started for its marked sedation properties. Clonidine is rapidly absorbed after oral administration with a time to maximum plasma concentration between 1.5 and 2 h [3] and has a half-life approximately 8–12 h [4,5]. This implies a possible place to target intra- and postoperative events.

This drug has been largely studied in anesthesia, suggesting a place for analgesia, antiemesis, bleeding reduction, induction time reduction, hemodynamic and hormonal stability, reduction of oxygen consumption, renal protection, anesthetics-sparing effect, anxiolysis, sedation, antishivering, recovery time reduction and myocardial protection.

The aim of these systematic review and meta-analyses is to systematically evaluate these potential indications of clonidine.

2. Methods

According to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) recommendations [6], we selected and analyzed the available literature published on PubMed/Medline and on the Cochrane database.

2.1. Information sources, eligibility criteria and study selection

We screened the PubMed/Medline (1966 – November 2014) and the Cochrane database using the terms “clonidine” AND (“anaesthesia” or “anesthesia”). We used the PICOS framework (patient, intervention, comparison, outcome and study design) as proposed in the PRISMA statement. Inclusion criteria included the facts that the studies were human randomized controlled trials involving adults (aged >18 years) who received systemic (oral, intramuscular, transdermal and intravenous) clonidine pre, per or postoperative undergoing local, regional or general anesthesia for every type of surgery, testing its different effects. As our goal was to evaluate all the potential indications of clonidine, no restriction was done on this field. Studies with no appropriate data reporting (e.g. size effect in term of mean response) were excluded from the quantitative analyses, and, eventually, from the qualitative analyses. Missing data were considered as such. All articles identified through the literature search were reviewed for inclusion by one author (MCSM) with the help of another author (PF). Queries were solved by consensus method between both authors (MCSM and PF).

2.2. Data collection

Firstly, one author (MCSM) screened the references identified by the search strategy by title and abstract. After the selection of the clear and complete references, relevant information from the original papers was extracted. Incomplete or unclear reports were excluded. Finally the second author involved in data collection (PF) independently checked the extracted data. The Cochrane Collaboration's tool was used for assessing risks of bias at the study level (including funnel plots). Only publications in English were included (for full methodology, see the Appendix).

2.3. Data extraction

Extracted information included authors, country, date of publication, study design, type of surgery, type of anesthesia, number of participants, age, ASA score, clonidine dose(s), route of administration and timing.

In addition for every single effect of the clonidine studied we extracted specific and relevant information, as detailed in the Appendix. Finally we also extracted data on adverse events.

2.4. Statistical analysis

A meta-analysis is typically a two-step process. Qualitative and quantitative analyses were performed sequentially on the different outcomes associated to the possible indications of clonidine. These outcomes were isolated from the studies identified as described above. For categorical outcomes, Mantel-Haenszel method was used, permitting to pool risk ratios as risk differences. Concerning mean differences, the fixed-effect mean difference for continuous outcomes was used. For these continuous outcomes, data are presented as mean, with their 95% confidence intervals. Heterogeneity was assessed by the I^2 statistics for each comparison. An $I^2 > 40\%$ was considered to reject the homogeneity of the comparison (and to accept heterogeneity hypothesis). For all the comparisons, a p-value < 0.05 was considered as statistically significant. In the cases of heterogeneity, random-effect models were used. Sensitivity analyses and random effect models were used to confirm the robustness of these methods (data not shown).

All the analyses were done using RevMan 5.3 (the Cochrane Collaboration, Oxford, UK).

3. Results

3.1. Studies' selection

We identified 775 trials and thereafter excluded 718. We analyzed 57 trials (Fig. 1) concerning 14,790 patients (ASA scored I to IV and aged between 18 and 93) of whom 7408 received clonidine (between 1 and 5 μg/kg), 6836 received placebo, 501 received others drugs and 45 were excluded. Demographic data showed there were no differences between the groups, regarding the age, the body weight, the ASA score and the gender in all the 57 trials. Per protocol, we considered the comparisons of all the studies, included these in the qualitative analyses (Table 2), and, if possible, we performed quantitative (meta-)analyses

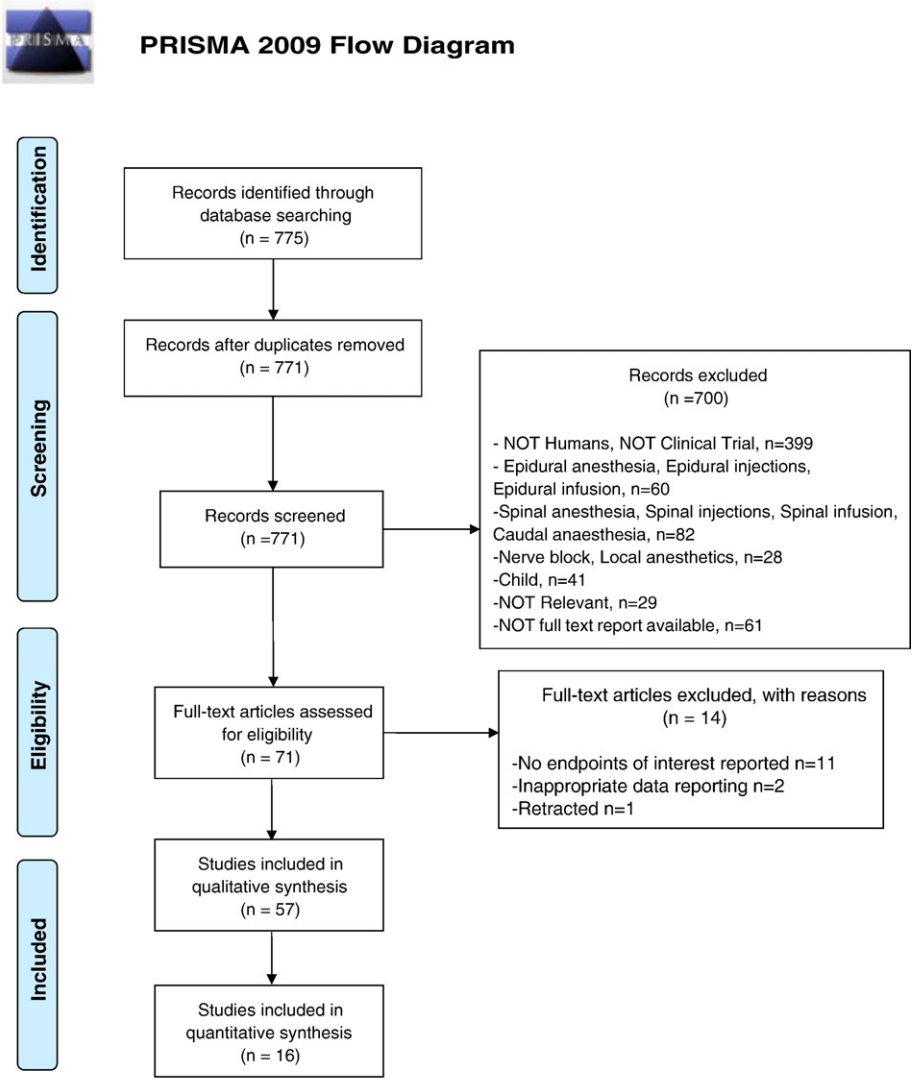

Fig. 1. PRISMA flow diagram.

Table 1
Included randomized controlled trials.

Reference	Country	Year	Type of study	Surgery	Type of anesth	Number of patients	Clonidine group	Placebo group	Other drugs	Excl	Doses	Via	Timing	Age	ASA score
Samantaray et al. [24]	India	2014	P, R, DB, Pl-C	Thoracic surgery	G	60	30	28	x	2	Clonidine 3 μg/kg vs placebo	IV	PER Op - 30 min pump	18–70	I–III
Singh et al. [25]	India	2011	P, R, SB, Pl-C	Laparoscopic cholecystectomy	G	50	25	25	x	x	Clonidine 150 μg vs placebo	Oral	PRE Op - 90 min before induction	20–60	I–II
Caumo et al. [26]	Brazil	2009	P, R, DB, Pl-C	Abdominal hysterectomy	G	59	19	20	20	x	Clonidine 100 μg vs melatonine 5 mg vs placebo	Oral	PRE Op - night before and 60 min before induction	19–60	I–II
Yu et al. [27]	Taiwan	2003	P, R, DB, Pl-C	Laparoscopic cholecystectomy	G	32	15	15	x	2	Clonidine 150 μg vs placebo	Oral	PRE Op – 60–90 min before induction	x	I–III
Marchal et al. [28]	Spain	2001	P, R, DB, Pl-C	Middle ear surgery	G	40	19	21	x	x	Clonidine 300 μg vs placebo	Oral	PRE Op - 90 min before induction	35–45	I–III
Dimou et al. [29]	Belgium	2003	P, R, DB, Pl-C	Abdominal hysterectomy	G	40	18	20	x	2	Clonidine 1 μg/kg vs placebo	T and IV	PRE Op - night before and 10 min before induction	20–59	I–II
Park et al. [30]	Canada	1996	P, R, DB, Pl-C	Total knee replacement or hemiarthroplasty	G	44	20	19	x	5	Clonidine 5 μg/kg vs placebo	Oral	PRE Op – 90 min before induction/POST op 12 h and 24 h	61–76	I–III
De Kock et al. [31]	Belgium	1992	P, R	Major abdominal surgery	G	200	96	91	x	13	Clonidine 4 μg/kg + 2 μg/kg/h vs placebo	IV	PRE Op - 30 min and PER Op pump	20–75	I–III
Jeffs et al. [32]	UK	2002	P, R, DB, Pl-C	Lower abdominal surgery	G	60	30	30	x	x	Clonidine 4 μg/kg vs placebo	IV	PER Op	18–75	I–II
Horn et al. [33]	USA and Austria	1997	P,R, Pl-C	Ear, nose and pharyngeal surgery	G	60	30	30	x	x	Clonidine 3 μg/kg vs placebo	IV	PER Op - 5 min before tracheal extubation	20–64	I–II
Yadav et al. [34]	India	2013	P, R, DB, Pl-C	Laparoscopic cholecystectomy	G	120	40	44	36	x	Clonidine 150 μg vs midazolam 15 mg vs placebo	Oral	PRE Op - 60 min before induction	18–60	I–II
Taheri et al. [35]	Iran	2010	P, R, DB, Pl-C	Ear surgery	G	60	30	30	x	x	Clonidine 4 μg/kg vs placebo	Oral	PRE Op - 60 min before induction	19–40	I
Oddly-Muhrbeck et al. [36]	Sweden	2002	P,R,DB, Pl-C	Breast cancer surgery	G	68	30	30	x	8	Clonidine 2 μg/kg vs placebo	IV	PRE Op - before induction	33–83	I–II
Taghipour et al. [9]	Iran	2012	P, R, DB, Pl-C	Lumbar spine surgery	G	30	15	15	x	x	Clonidine 200 μg vs placebo	Oral	PRE Op – 60–90 min before induction	20–65	I–II
Mohseni et al. [37]	Iran	2011	P, R, Pl-C	Endoscopic sinus surgery	G	84	42	42	x	x	Clonidine 200 μg vs placebo	Oral	PRE Op - 90 min before induction	23–57	I–II
Watanabe et al. [14]	Japan	2006	P, R, DB, Pl-C	Abdominal hysterectomy or oophorectomy	G	84	41	40	x	3	Clonidine 150 μg vs 300 μg vs placebo	Oral	PRE Op - 90 min before induction	19–60	I–II
Inomata et al. [38]	Japan	1999	P, R, SB	Surgical procedures	G	104	52	52	x	x	Clonidine 4.5 μg/kg vs no medication	Oral	PRE Op - 90 min before induction	30–48	I
Singhal et al. [12]	India	2014	P, R, DB	Elective surgery	G	100	50	x	50	x	Clonidine 200 μg vs gabapentin 900 mg	Oral	PRE Op - 90 min before induction	20–50	I–II
Mujahid-ul-Islam et al. [39]	Pakistan	2012	P, R, DB, Pl-C	Surgical procedures	G	60	28	29	x	3	Clonidine 200 μg vs placebo	IV	PRE Op - 90 min before surgery	40–65	I–III
Montazeri et al. [40]	Iran	2011	P, R, DB,	Elective surgery	G	96	32	32	32	x	Clonidine 300 μg vs gabapentin 800 mg vs placebo	Oral	PRE Op - 90 min before surgery	18–65	I–II

(continued on next page)

Table 1 (*continued*)

Reference	Country	Year	Type of study	Surgery	Type of anesth	Number of patients	Clonidine group	Placebo group	Other drugs	Excl	Doses	Via	Timing	Age	ASA score
Sammenakousar et al. [41]	India	2013	P, R	Elective non-cardiac surgery	G	150	50	50	50	x	Clonidine 2 μg/kg vs fentanyl 2 μg/kg vs placebo	IV	PRE Op - 5 min before laryngoscopy	20–60	I–II
Talebi et al. [42]	Iran	2010	P, R, DB, Pl-C	Elective surgery	G	274	137	137	x	x	Clonidine 200 μg vs placebo	Oral	PRE Op – 90–120 min before surgery	18–45	I–II
Doak et al. [43]	Canada	1993	P, R, DB, Pl-C	Elective orthopedic or abdominal surgery	G	42	14	14	14	x	Clonidine 5 μg/kg vs diazepam 0.15 mg/kg vs placebo	IV	PRE Op - 90 min before induction	>45	I–II
Gupta et al. [44]	India	2011	P, R, SB, Pl-C	Laparoscopic cholecystectomy	G	180	60	60	60	x	Clonidine 200 μg vs 150 mg pregabalin vs placebo	Oral	PRE Op – 75–90 min before surgery	35–52	I–II
Tripathi et al. [45]	India	2011	P, R, DB, Pl-C	Laparoscopic cholecystectomy	G	90	60	30	x	x	Clonidine 1 or 2 μg/kg vs placebo	IV	PRE Op - 30 min before induction	20–60	I–II
Kalra et al. [46]	India	2011	P, R, DB, Pl-C	Laparoscopic cholecystectomy	G	120	60	27	29	4	Clonidine 1 or 1.5 μg/kg vs 50 mg/kg magnesium vs placebo	IV	PER Op - over 15 min after induction and before pneumoperitoneum	29–51	I
Kalajdzija et al. [47]	Bosnia and Herzegovina	2011	P, R, Pl-C	Elective non-cardiac surgery	G	60	30	30	x	x	Clonidine 0.2 μg/kg/min vs placebo	IV	PER Op	30–60	I–II
Schneemilch et al. [48]	Germany	2006	P, R, DB, Pl-C	Carotid e endarterectomy	R	80	40	40	x	x	Clonidine 1 μg/kg + 1 μg/kg/h vs placebo	IV	PRE Op after RA and PER Op until skin closure	39–83	x
Hahm et al. [49]	Korea	2002	P, R, DB, Pl-C	Knee, ear and nose surgery	G	44	22	22	x	x	Clonidine 300 μg vs placebo	Oral	PRE Op - 120 min before induction	20–50	I–II
Howie et al. [50]	USA	1996	P, DB, Pl-C	Coronary artery bypass graft surgery	G	54	28	26	x	x	Clonidine 5 μg/kg + 5 μg/kg vs placebo	Oral	PRE and PER Op - 90 min before induction and 30 min before cardiopulmonary bypass	50–75	III–IV
Ellis et al. [16]	USA	1994	P, R, DB, Pl-C	Elective major non cardiac surgery	G	61	30	31	x	x	Clonidine 0.2 mg/day patch for 3 days + 0.3 mg vs placebo	T and Oral	PRE, PER and POST Op (0.2 mg/d patch) and PRE Op 90 min before induction (0.3 mg)	61–75	x
Taittonen et al. [51]	Finland	1998	P, R, DB, Pl-C	Elective plastic surgery	G	30	10	10	10	x	Clonidine 2 μg/kg vs midazolam 70 μg/kg vs placebo	IM	PRE Op – 40–50 min before induction	27–57	I
Taittonen et al. [52]	Finland	1997	P, R, DB, Pl-C	Elective plastic surgery	G	30	10	10	10	x	Clonidine 4 μg/kg vs dexmedetomidine 2.5 μg/kg vs placebo	IM	PRE Op – 40–50 min before induction	19–56	I
Von Montigny et al. [53]	Belgium	1998	P, R, DB	Colon resection surgery	G	60	15	15	30	x	Clonidine 4 μg/kg + 2 μg/kg/h vs sufentanil 0.2 μg/kg/h vs ketamine 0,5 mg/kg + 0,25 mg/kg/h vs bupivacaine 5% 7 ml +5 ml/h	IV	PER Op	50–67	x
Vahabi et al. [54]	Iran	2010	P, R, DB, Pl-C	Cystocele-rectocele perineorrhaphy surgery	G	60	30	30	x	x	Clonidine 5 μg/kg vs placebo	Oral	PRE Op - 90 min before induction	20–40	I–II
Laisalmi et al. [55]	Finland	2001	P, R, DB, Pl-C	Laparoscopic cholecystectomy	G	30	15	15	x	x	Clonidine 4.5 μg/kg vs placebo	IM	PRE Op	32–56	x
Hamaya et al. [56]	Japan	1994	P, R, Pl-C	Otorhinolaryngologic or orthopedic surgery	G	57	38	19	x	x	Clonidine 5 μg/kg vs 2.5 μg/kg vs placebo	Oral	PRE Op - 90 min before induction	34–43	I–II
Moghadam et al. [57]	Iran	2011	P, R, SB, Pl-C	Elective leg surgery	G	160	80	80	x	x	x	x	x	18–65	I–II
Ghosh et al. [58]	India	2008	P, R, SB, Pl-C	Peripheral nerve repair surgery	G	90	30	30	30	x	Clonidine 200 μg vs metoprolol 100 mg vs placebo	Oral	PRE Op - 60 min before surgery	18–60	I–II
Morris et al. [59]	Australia	2005	P,R,DB, Pl-C	Lower extremity vascular surgery	G	39	21	18	x	x	Clonidine 3 μg/kg vs placebo	Oral	PRE Op - 60 min before surgery	43–93	II–III
Fehr et al. [60]	Switzerland	2001	P, R,	Superficial surgical	G	50	25	25	x	x	Clonidine 4 μg/kg vs placebo	IV	PER Op - 10 min infusion	18–70	I–II

			DB, Pl-C	procedures										
Goyagi et al. [61]	Japan	2000	P, R, Pl-C	Total abdominal hysterectomy	G	41	22	19	x	x	Clonidine 5 μg/kg vs placebo	Oral	PRE Op - 90 min before induction	25–61	I–II
Goyagi et al. [62]	Japan	1999	P,R,Pl-C	Elective gynecological surgery	G and E	39	19	20	x	x	Clonidine 5 μg/kg vs placebo	Oral	PRE Op - 90 min before induction	35–55	I–II
Imai et al. [63]	Japan	1998	P, R, DB	Breast cancer surgery	G	80	40	20	20	x	Clonidine 75 μg vs 150 μg vs diazepam 10 mg vs placebo	Oral	PRE Op - 60 min before induction	36–64	I–II
Katoh et al. [64]	Japan	1997	P, R, Pl-C	Elective oral or nasal surgery	G	42	21	21	x	x	Clonidine 5 μg/kg vs placebo	Oral	PRE Op - 60 min before induction	20–60	I–II
Buggy et al. [19]	Ireland	1997	P, R	Elective, short (<90 min) peripheral surgery	G	60	30	30	x	x	Clonidine 150 μg vs placebo	IV	PRE Op - before induction	16–65	I–II
Jabbary et al. [65]	Iran	2013	P, R, Pl-C	Elective leg fracture procedures	G	160	80	80	x	x	Clonidine 5 μg/kg vs placebo	Oral	PRE Op - 90 min before surgery	18–65	I–II
Vanderstappen et al. [66]	Belgium	1996	P, R, DB, Pl-C	Elective peripheral surgery	G	280	140	140	x	x	Clonidine 2 μg/kg vs placebo	IV	PER Op - 10 min after induction	23–41	I–II
Sia [67]	Italy	1998	P, R	Knee arthroscopy	E	100	50	50	x	x	Clonidine 1 μg/kg vs placebo	IV	PRE Op - just before epidural anesthesia	18–44	I–II
Schwarzkopf et al. [68]	Germany	2001	P, R, DB	Laparoscopic or orthopedic surgery	G	60	20	x	40	x	Clonidine 150 μg vs 25 mg meperidine vs 25 mg urapidil	IV	POST Op - after 5 min continuous shivering	22–55	I–II
Shukla et al. [69]	India	2011	P, R, DB	Various surgical procedures	S	80	40	x	40	x	Clonidine 0.5 μg/kg vs 0.5 μg/kg tramadol	IV	POST Op	18–45	I
Rocha et al. [70]	Brazil	2011	P, R, DB	Heart catheterization	Se	60	30	x	30	x	Clonidine 0.5 μg/kg vs 0.1 μg/kg sufentanil	IV	PRE Op - before heart catheterization	18–80	III
Filos et al. [22]	Greece	1993	P, R, DB, Pl-C	Elective ophthalmicus surgery	L and Se	60	40	20	x	x	Clonidine 150 μg vs 300 μg vs placebo	Oral	PRE Op - the morning of the operation	65–82	I–III
Deveraux et al. [1]	23 Countries	2014	P, R, Pl-C	Non-cardiac Surgery	G, E, R, S	10,010	5009	5001	x	x	Clonidine 200 μg/day patch during 3 days vs placebo	Oral/T	PRE Op - before induction	58–79	x
Singh et al. [71]	India	2013	P, R, DB	Elective laparoscopic cholecystectomy	G	80	40	40	x	x	Clonidine 2 μg/kg IV vs clonidine 2 μg/kg IM	IV vs IM	PRE Op – 60–90 min before surgery	20–60	I–II
De Kock et al. [72]	Belgium	1994	P, R, Pl-C	Major abdominal surgery	G	402	350	52	x	x	Clonidine 4 μg/kg + 2 μg/kg/h vs placebo	IV	PER Op - at the induction	72–34	I–IV
Maruyama et al. [29]	Japan	2004	P, R, Pl-C	Lower limb surgery with tourniquet	Se	24	10	11	x	3	Clonidine 5 μg/kg vs placebo	IV	PRE Op - 60 min before the operation	61–24	x

x = no data available/P = prospective/R = randomized/Pl-C = placebo controlled/BS = simple blind/DS = double blind.
G = general/E = epidural/R = other regional/S = spinal/Se = sedation/L = local.
IV = intravenous/IM = Intramuscular/T = transdermal.
Type anesth = type of anesthesia.
Excl = excluded.
Via = route of administration.
ASA score = American Association of Anesthesiology score.
Op = operative.

Table 2
Qualitative analyses of randomized controlled trials on the effect of clonidine vs placebo.

Indication	Number of studies	Clonidine group	Placebo/control group	Positive studies	Negative studies
First analgesic intake/time to first analgesic	4	100	98	3	1
Pain scores at 24 h	7	161	163	2	5
Analgesic consumption at 24 h	9	272	269	8	1
Postoperative nausea and vomiting prevention	6	180	217	6	0
Bleeding control	3	76	78	3	0
Inhalatory induction time	2	93	92	2	0
Heart rate reduction after tracheal intubation (1 min)	7			5	2
Mean arterial pressure reduction after tracheal intubation (1 min)	6			4	1
Hormonal and catecholaminergic stability	6	201	209	6	0
Preoperative oxygen consumption reduction	2	20	20	2	0
Intraoperative oxygen consumption reduction	3	35	35	1	2
Postoperative oxygen consumption reduction	2	20	20	1	1
Increased diuresis	2	68	49	2	0
Decreased renin activity	2	45	45	2	0
Shivering incidence reduction	6	360	360	6	0
Shivering treatment	2	60	80	1	1
Sedation and anxiolysis	10	402	453	8	2
Patients'satisfaction	5	145	158	5	0
Cardiac protection	2	5039	5032	0	2

(detailed studies characteristics, including the route of administration, in the Table 1 and in the Appendix).

3.2. Data analyses (for details, see the Appendix)

3.2.1. Does clonidine improve postoperative analgesia?

Data of postoperative analgesia were reported in 10 trials including 645 patients (302 received clonidine, 299 placebo, 20 melatonine and 29 were excluded). First analgesic intake/time to first analgesic (FAI/TAR) were reported in 4 trials and pain scores (visual analgesic scale, VAS, at 12, 24 and 48 h) in 7 trials. Pain scores at rest were not reduced in the majority of the studies (Variability in scales types precluded any quantitative analysis). In contrast, cumulative analgesic consumption was reduced at 24 h and 36 h. Four trials were included in the quantitative analysis, showing a reduction of analgesics consumption after 24 h (reduction of 24%, 95%CI[16%–32%])($p < 0.001$) (Fig. 2).

3.2.2. Does clonidine reduce postoperative nausea and vomiting?

Data of PONV were reported in 6 trials including 412 patients (180 received clonidine, 181 placebo, 36 midazolam and 15 were excluded). The incidence of PONV was significantly reduced by clonidine in all the 6 trials (risk ratio: 0.35, 95%CI[0.25–0.51])($p < 0.001$) (Fig. 3). Antiemetics rescue at 24 h was reported, and reduced, in 1 trial.

3.2.3. Does clonidine reduce intraoperative bleeding?

Intraoperative bleeding was investigated in 3 trials including 154 patients (76 received clonidine, 78 placebo). Blood loss was reported, and significantly reduced, in 2 trials. As these data were heterogeneous ($I^2 = 91\%$), a random-effect model was used, but did not permit to confirm a significant difference (mean difference: −168.6 ml [−453.7–116.5])($p = 0.25$) (Fig. 4). Variable type of bleeding scores were reported, and significantly reduced, in 2 trials. Surgeon satisfaction score was reported in 2 trials showing statistically a significant improvement in one of them.

3.2.4. Does clonidine reduce induction time?

Data of induction time were reported (only for general anesthesia) in 2 trials including 188 patients (93 of them received clonidine, 92 placebo). Induction time was recorded, and significantly reduced, in 2 trials. As these data were heterogeneous ($I^2 = 86\%$), a random-effect model was used, showing a statistically significant difference (mean difference: −12.72 s [−21.5–3.9])($p = 0.005$) (Fig. 5).

3.2.5. Does clonidine improve hemodynamic stability?

Data of hemodynamic stability were reported in 10 trials, in which 7 reported hemodynamic data for tracheal intubation response, including

Table 3
Randomized controlled trials on the effect of clonidine vs placebo on anesthetic-sparing effect.

Reference	Number of patients	Clonidine group	Placebo group	Narcotic-sparing effect
Moghadam et al. [57]	160	80	80	$p < 0.0001$ propofol
Ghosh et al. [58]	90	30	30	$p < 0.001$ propofol
Morris et al. [59]	39	21	18	$p < 0.05$ propofol
Laisalmi et al. [55]	30	15	15	$p < 0.05$ alfentanil
Fehr et al. [60]	50	25	25	$p < 0.001$ propofol/NS remifentanil
Goyagi et al. [61]	41	22	19	$p = 0.0013$ propofol
Goyagi et al. [62]	39	19	20	$p < 0.05$ propofol
Imai et al. [63]	80	40	20	$p < 0.01$ propofol
Katoh et al. [64]	42	21	21	$p < 0.001$ sevoflurane
Howie et al. [50]	54	28	26	$p < 0.04$ sufentanil/$p < 0.01$ sevoflurane
Singh et al. [25]	50	25	25	$p < 0.05$ isoflurane
Oddly-Muhrbeck et al. [36]	68	30	30	$p < 0.04$ propofol/$p < 0.01$ sevoflurane
Taghipour et al. [9]	30	15	15	$p < 0.001$ remifentanil
Marchal et al. [28]	40	19	21	$p < 0.001$ isoflurane/$p < 0.001$ fentanyl/NS propofol
Inomata et al. [38]	104	52	52	$p = 0.0001$ sevoflurane
Kalajdzija et al. [47]	60	30	30	$p < 0.001$ sevoflurane/NS fentanyl
Ellis et al. [16]	61	30	31	$p < 0.05$ enflurane
Hamaya et al. [56]	57	38	19	$p < 0.05$ isoflurane

NS = not statistically significant difference.

Table 4
Randomized controlled trials on the effect of clonidine vs placebo on safety and adverse events.

Reference	Number of patients	Clonidine group	Placebo group	Hypotension	Bradycardia	Others adverse events
Marchal et al. [28]	40	19	21	NS	NS	NS
Singh et al. [25]	50	25	25	x	x	No adverse events
Samantaray et al. [24]	60	30	28	NS	NS	NS
De Kock et al. [31]	200	96	91	x	x	No adverse events
Oddly-Muhrbeck et al. [36]	68	30	30	x	x	No adverse events
Taghipour et al. [9]	30	42	42	x	NS	NS
Mohseni et al. [37]	84	42	42	NS	NS	NS
Watanabe et al. [14]	84	41	40	x	x	NS
Inomata et al. [38]	104	15	15	x	x	No adverse events
Singh et al. [71]	80	40	40	NS	NS	Hypertension (—C)
Gupta et al. [44]	180	60	60	x	x	No adverse events
Tripathi et al. [45]	90	60	30	x	x	No adverse events
Kalra et al. [46]	120	60	27	NS	x	No adverse events
Singh et al. [25]	50	25	25	NS	NS	No adverse events
Imai et al. [63]	80	40	20	0	0	No adverse events
Filos et al. [22]	60	40	20	$p < 0.001$ (+C)	$p < 0.05$ (+C)	No adverse events
De Kock et al. [72]	402	350	52	$p < 0.01$ (—C)	NS	x
Maruyama et al. [29]	24	10	11	$p < 0.05$ (+C)	x	x
Singhal et al. [12]	100	50	50	NS	NS	No adverse events
Mujahid-ul-Islam et al. [39]	60	28	29	x	x	No adverse events
Montazeri et al. [40]	96	32	32	NS	NS	No adverse events
Kalajdzija et al. [47]	60	30	30	x	x	Others (—C)
Schneemilch et al. [48]	80	40	40	x	x	Others (—C)
Hahm et al. [49]	44	22	22	x	x	HypoK (—C)
Howie et al. [50]	54	28	26	NS	NS	NS
Ellis et al. [16]	61	30	31	x	x	NS
Ghosh et al. [58]	90	30	30	x	x	No adverse events
Morris et al. [59]	39	21	18	NS	NS	No adverse events
Fehr et al. [60]	50	25	25	x	x	No adverse events
Goyagi et al. [61]	90	19	20	NS	NS	NS
Shukla et al. [69]	80	40	x#	NS	NS	NS
Deveraux et al. [1]	10,010	5009	5001	$p < 0.001$ (+C)	$p = 0.02$ (+C)	NS

X = no data available/NS = not statistically significant differences.
+C = more in clonidine group/–C = less in clonidine group.
= 40 received other drug (tramadol).

772 patients (336 received clonidine, 287 placebo, 146 other drugs as fentanyl (50), gabapentin [72] or diazepam [14] and 3 were excluded).

Heart rate (HR) was reported in 7 trials showing a statistically significant reduction 1 min after intubation (in 4 of 6 trials). HR was found also significantly reduced after intubation (5 trials). Three trials were included in the quantitative analysis, showing a reduction of the HR 1 min after intubation (reduction of 14.9 bpm, 95%CI[10.4–19.5]; $p < 0.001$) (Fig. 6).

Mean arterial pressure (MAP) was reported in 6 trials showing statistically significant reduction 1 min after intubation (in 4 of 5 trials). Three trials were included in the quantitative analysis, showing a reduction of the MAP 1 min after intubation (reduction of 12.5 mm Hg, 95%CI[7.14–17.86]; $p < 0.001$) (Fig. 7).

Four trials reported hemodynamic data in laparoscopic surgeries including 440 patients (205 received clonidine, 142 placebo, 89 received other drugs as pregabalin [60] or magnesium [29] and 4 were excluded). HR was significantly reduced 1 min after insufflation (one trial) as MAP.

3.2.6. Does clonidine improve hormonal stability and catecholamine secretion?

Data of hormonal stability and catecholamine secretion were reported in 7 trials including 413 patients (201 received clonidine, 199 placebo, 10 midazolam and 3 were excluded). Epinephrine plasma concentrations were significantly reduced by clonidine in all the 6 relevant trials, and norepinephrine concentrations in 5 of 6 trials. As the

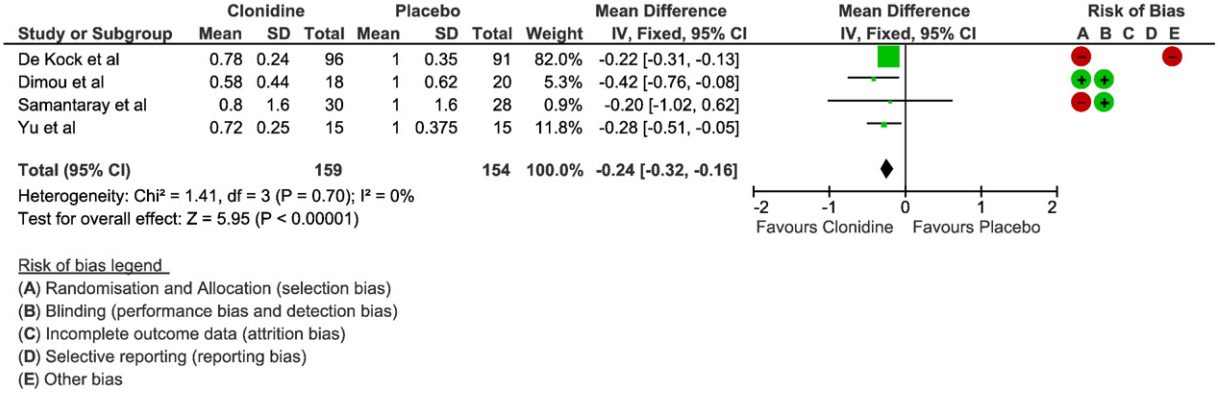

Fig. 2. Forest plot for analgesic consumption during the 24 first postoperative hours in randomized-controlled trials comparing clonidine vs placebo (0 correspond to the reference/placebo, ±1 means ±100% of the analgesics consumption). For risks of biases: + = low risk; − = high risk; blank = unclear.

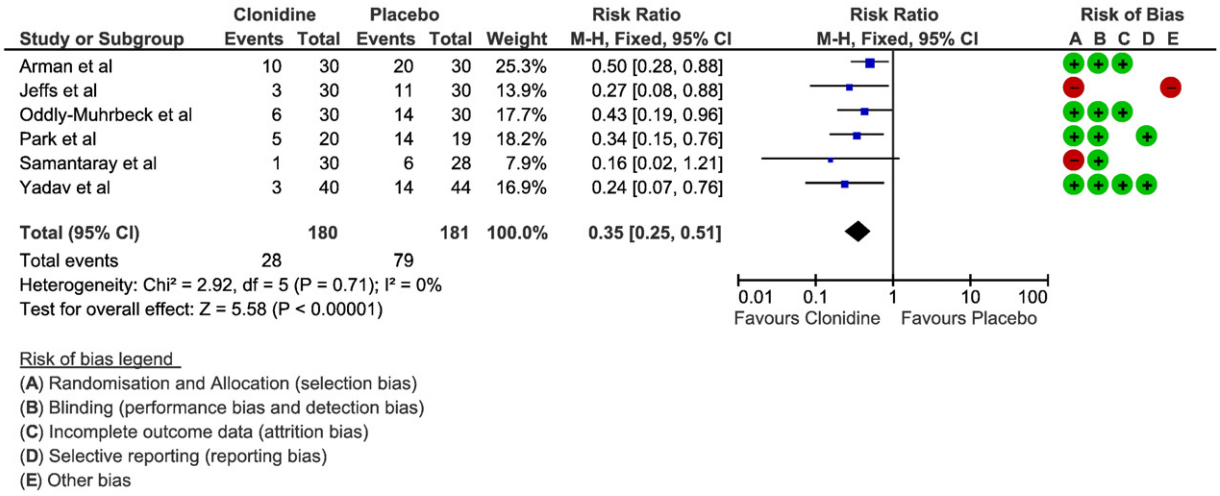

Fig. 3. Forest plot for reduction of incidence of nausea and vomiting during the 24 first postoperative hours in randomized-controlled trials comparing clonidine vs placebo. For risks of biases: + = low risk; − = high risk; blank = unclear.

methods used were different in these studies, no quantitative analyses were considered as valid.

3.2.7. Does clonidine reduce oxygen consumption?

Data on oxygen consumption were reported in 3 trials including 120 patients (35 received clonidine, 35 placebo, 50 others drugs as midazolam [10], dexmedetomidine [10], sufentanil [10], ketamine [10] or bupivacaine [10]). Preoperative oxygen consumption was significantly reduced in the 2 trials and intraoperative oxygen consumption was significantly reduced in 1 of 3 trials, and in 1 of 2 trials postoperatively. But differences in the design of the studies precluded any aggregation in a meta-analysis.

3.2.8. Does clonidine modify renal function?

Data on renal function were reported in 3 trials including 147 patients (83 received clonidine, 64 placebo). Urine output was significantly increased, and plasma renin activity decreased, in the 2 trials reporting these. Regarding the different time points used, no aggregated analysis was possible.

3.2.9. Does clonidine have an anesthetics-sparing effect?

Data of anesthetics-sparing effect were reported in 18 trials including 1095 patients (540 received clonidine, 497 placebo, 50 received other drugs as diazepam [20] or metoprolol [30] and 8 were excluded). Anesthetics consumption as propofol [9], sevoflurane [5], isoflurane [3], enflurane [1], alfentanil [1], sufentanil [1], remifentanil [1] was reported in 18 trials. Anesthetics use was significantly reduced in all the trials. Regarding heterogeneity of the comparisons, we did not perform any quantitative analysis, but reported these into the Table 3.

3.2.10. Does clonidine reduce postoperative shivering?

Data of shivering were reported in 7 trials. In 5 of the trials clonidine was given in prophylaxis, including 660 patients (330 received clonidine and 330 placebo). Incidence of shivering was significantly reduced in the 5 trials. Severity of shivering was reported in the 2 trials reporting it. Three trials were included in the quantitative analysis, showing a reduction of the incidence of shivering (risk ratio: 0.17, 95%CI[0.10–0.29]; $p < 0.001$) (Fig. 8).

3.2.11. Does clonidine improve sedation and anxiolysis?

Data of sedation and anxiolysis were reported in in 10 trials including 858 patients (402 received clonidine, 257 placebo, 196 other drugs as sufentanil [30], diazepam [20], gabapentin [50], midazolam [36], pregabalin [60] and 3 patients were excluded). Ramsay score for sedation, OAAS, VAS score for sedation and for anxiety or sedative and anxiety score were significantly decreased in 8 of the 10 trials. Regarding the variability of the used scores, no meta-analysis was performed.

3.2.12. Does clonidine modify recovery time?

Data on recovery time were reported in 11 trials including 961 patients (431 received clonidine, 394 placebo, 121 other drugs as gabapentin [32], pregabalin [60], magnesium [29] and 15 patients were excluded). Time in recovery room was reported in 6 trials, with no significant difference in 5 but, in 1, time was significantly reduced by clonidine. Considering the data heterogeneous ($I^2 = 71\%$), a random-effect model was used, not showing any statistically significant difference (mean difference: 6.3 min [−4.8–17.4])($p = 0.26$) (Fig. 9). Times to eyes opening, extubation, name, age and date of birth declaration, response to verbal commands, complete arousal and awakening were reported respectively in 16 trials showing statistically significant results in different items in 12 of them: 9 reported better results for clonidine and 3 worse in clonidine.

3.2.13. Does clonidine modify patients' satisfaction?

Data on patients' satisfaction were reported in 5 trials, in relation to PONV, pain, sedation or anesthesia quality, including 314 patients (145

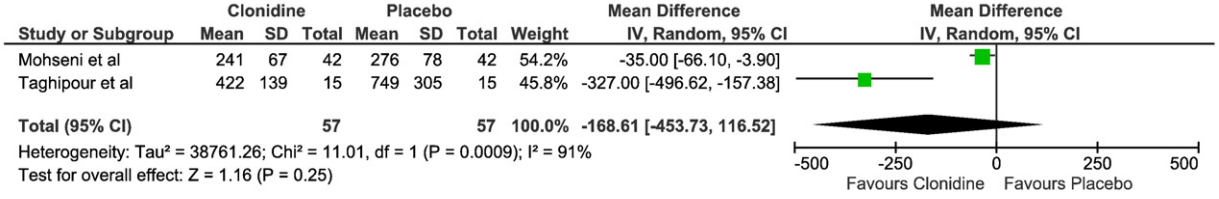

Fig. 4. Forest plot for intraoperative bleeding reduction, in randomized-controlled trials comparing clonidine vs placebo. For the two trials, risks of biases are unclear (blank).

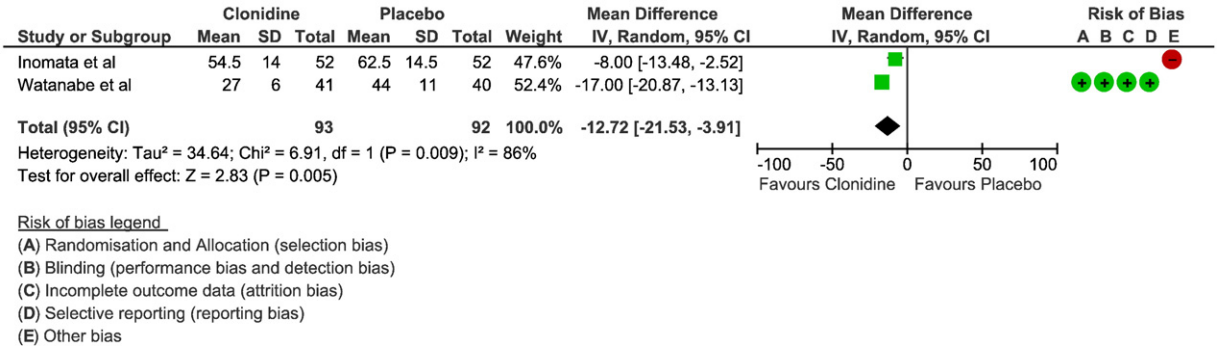

Fig. 5. Forest plot for reduction of induction time, in randomized-controlled trials comparing clonidine vs placebo. For risks of biases: + = low risk; − = high risk; blank = unclear.

received clonidine, 114 placebo, 44 other drugs as sufentanil [30] or diazepam [14] and 11 patients were excluded). Level of satisfaction was significantly better in all the 5 trials in the clonidine group. Due to various used scales, no meta-analysis was performed.

3.2.14. Does clonidine protect the heart?

Data of cardiac protection were reported in 2 trials including 10,071 patients (5039 received clonidine and 5032 placebo). Cardiac outcome was reported in 2 trials, including the POISE-2 trial. In these trials, cardiac ischemia was differently considered, and, in the POISE-2 trial, only myocardial infarction was reported (and not elevation of troponin or creatinine-kinase MB), precluding an aggregated analysis. No statistically significant differences were found between the groups.

3.2.15. Does clonidine induce adverse events and is it safe?

Data on adverse events and safety were reported in 32 trials including 12,720 patients (6429 received clonidine, 5973 placebo, 261 other drugs as tramadol [40], diazepam [20], magnesium [29], pregabalin [60], metoprolol [30] and gabapentin and 36 exclusions were recorded)(Table 4). Bradycardia was reported in 15 trials, results in 14 of the trials were not statistically significant but well in the POISE-2 trial, including the majority of the patients. Hypotension was reported in 15 trials, results in 13 trials were not statistically significant but, similarly, well in the POISE-2 trial. Other adverse events were hypertension in non-clonidine patients (1 trial). When performing an aggregated analysis, no difference was identified, in terms of adverse events rates, between clonidine and placebo (0.00 [−0.10–0.11])($p = 0.96$) (Fig. 10). Nevertheless, various definitions (i.e. occurrence of hypotension) of these events render the interpretation difficult, as reflected by the high heterogeneity, leading to the use of a random-effect model ($I^2 = 99\%$). No other adverse event was reported as related to clonidine.

4. Discussion

These systematic review and meta-analyses of 57 trials was made to evaluate the available literature on indications of clonidine during the perioperative period. Different outcomes of clonidine in anesthesia were studied, in different series representing, in total, nearly 15,000 patients. It appears that clonidine reduces analgesics consumption, reduces PONV, improves hemodynamic and sympathetic stabilities, prevents postoperative shivering, and may reduce blood losses, induction time in inhalation anesthetic technique, without identified any influence on renal and cardiac outcomes or prolonged awakening time. Clonidine improves patient's satisfaction, associated with some of these items.

More in details, clonidine reduces FAI/TAR and VAS in the first 12 h, decreases analgesic consumption at least during the first 36 postoperative hours.

PONV is a common, distressing side effect of anesthesia and surgery [7]. All the trials analyzed showed that clonidine reduces PONV incidence and 24 h antiemetic rescue.

Clonidine does not alter laboratory blood coagulation [8] and seems to even reduce bleeding. Hemodynamic stability and surgeon's comfort may shorten the operating time, which further decreases bleeding [9,10].

Induction time is a factor of success a inhaled induction anesthetic technique [11] and is may be reduced by clonidine.

Hemodynamic stability is better achieved after tracheal intubation with clonidine, considering tachycardia and arterial pressure, both considered as potentially deleterious, even if the consequences of these events were not considered here [12–14]. Hemodynamic consequences of laparoscopic surgery, increasingly used [15], are reduced with clonidine. To note that the term “stability” used in the present quantitative and qualitative review is mainly focusing on time after intubation and insufflation. Of course, as consequences of hemodynamic variations

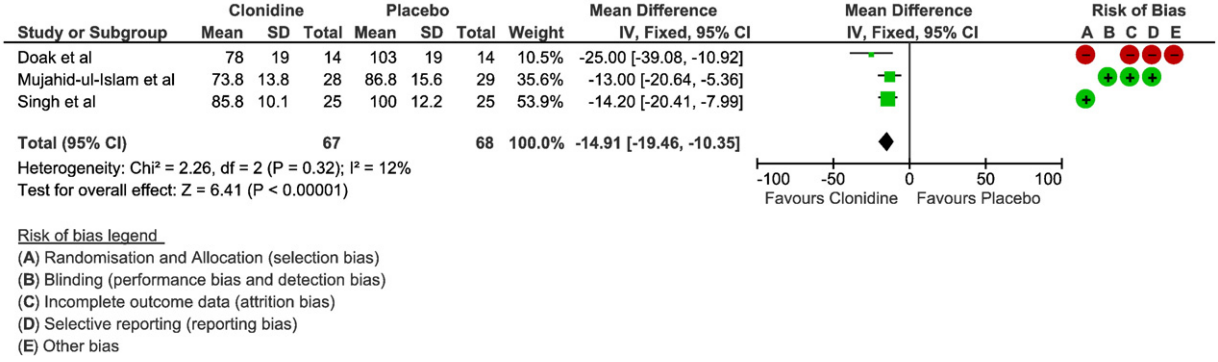

Fig. 6. Forest plot for reduction of heart rate, 1 min after intubation, in randomized-controlled trials comparing clonidine vs placebo. For risks of biases: + = low risk; − = high risk; blank = unclear.

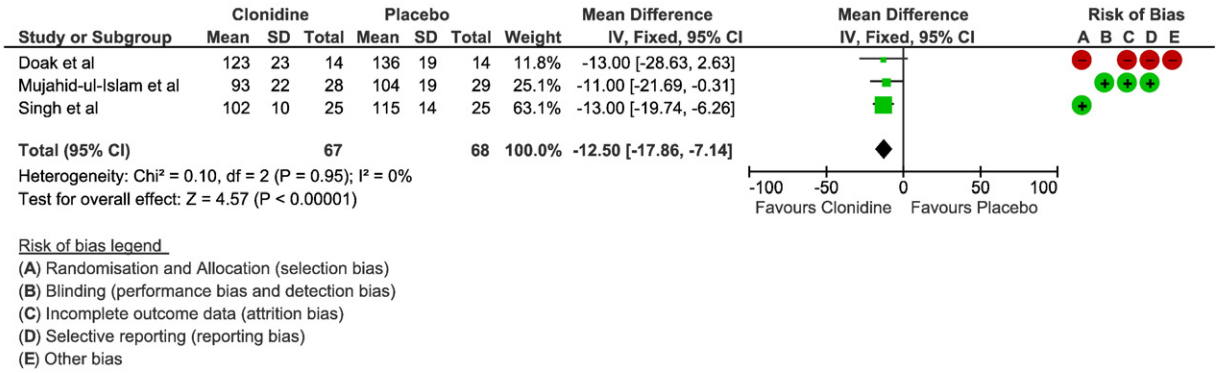

Fig. 7. Forest plot for reduction of mean arterial pressure, 1 min after intubation, in randomized-controlled trials comparing clonidine vs placebo. For risks of biases: + = low risk; − = high risk; blank = unclear.

are not limited to these periods, the occurrence of these events merits further discussion, especially regarding its safety (detailed later in the text).

In the same way the hormonal and catecholaminergic responses to surgery [16] is attenuated by clonidine.

Whether the reduction of this endocrine response, linked to an increase of arterial pressure, heart rate and oxygen consumption [17] permits to clonidine to reduce perioperative metabolic demands is not clear in this study.

There are many factors affecting renal function during anesthesia and surgery including renal blood flow, blood volume and endocrine system activity, all of these potentially influenced by clonidine. It appears that, even if clonidine can be associated with a reduced arterial pressure, the net effect on renal function appears to be neutral or positive, and not negative.

Avoiding unnecessary costs while improving or maintaining quality care is one goal in anesthesia [18] that can be achieved with clonidine, either considering volatile agents or intravenous anesthetics.

Postoperative shivering, a common cause of discomfort as a trigger to other deleterious complications [19] is reduced by clonidine, but seemingly better in prophylaxis than in treatment. In spite of the heterogeneity of the assessment methods, clonidine may have advantages in term of anxiolysis and sedation quality than the other drugs commonly used. As ambulatory surgery and diagnostic procedures under anesthesia require fast rehabilitation for early hospital discharge, awakening times with clonidine has retain attention. The results in the available literature show no differences, and some trials suggest even a shorter time.

Myocardial infarction is a major vascular complication of surgery and is associated with substantial mortality [20]. But, even if reducing potentially deleterious sympathetic activation, clonidine does not improve cardiac outcome.

Clonidine is a safe drug as is shown in the results of trials included in this review. In contrast it is important to not elude the fact that non-fatal bradycardia/non-fatal cardiac arrest and hypotension have been described. And, even if no sequels have been reported, it should be assumed that not enough data concerning bradycardia/non-fatal cardiac arrest are available to formally conclude about their safety. Concerning hypotension, as hypotension has been described as deleterious in large trials, included POISE-2. But, in contrast, clonidine-induced hypotension has never been specifically described as linked to classical adverse events linked to hypotension (worse renal or cardiac outcomes). Logically, it could be argued (even if not formally demonstrated here) that hypotension due to other factors than clonidine (e.g. hypovolemic shock) is problematic, but not necessarily if specifically due to clonidine.

Clonidine influences the effects of vasopressor and inotropic drugs, effects that would merits further studies [21]. Clonidine has to be used carefully in the elderly patient adjusting the dose [22] as in predicted hypotensive response as after tourniquet deflation [23].

To note that, linked to the design, at least in quantitative analyses, limitations of this work include the influence of interfering factors. We didn't include, for example, doses and patients ages as possible interfering factors. The determination of these specific factors' influence would merit further works. Another limitation is the fact that, as the analyzed endpoints were typically primary outcomes (even if not always) of the studies, many of these endpoints were not analyzed on all the 14,790 included patients. Moreover, an additional limitation is the variable doses and route, not included in subgroups analyses, even if logical considering the variability of patients, procedures and indications. Regarding separated analyses by route of administration, seeing the high

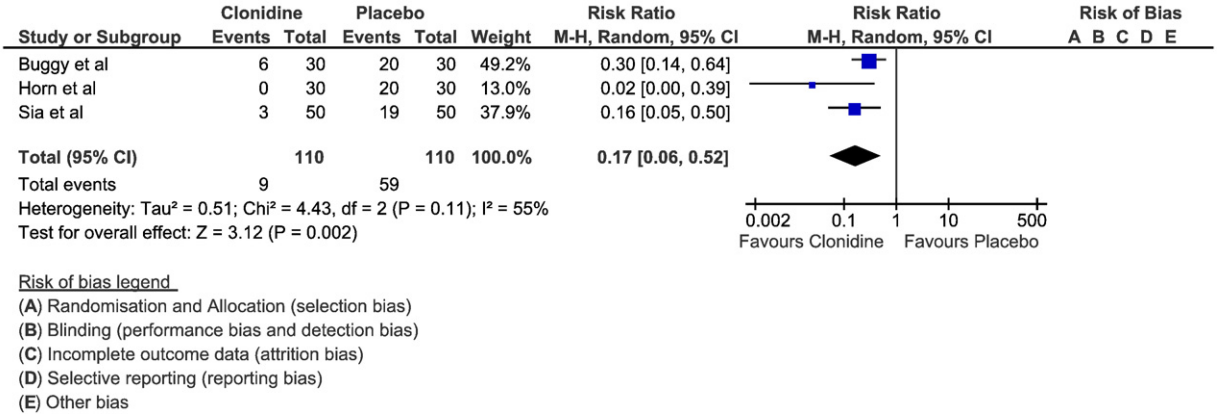

Fig. 8. Forest plot for reduction of incidence of postoperative incidence of shivering, in randomized-controlled trials comparing clonidine vs placebo. For all the trials, risks of biases are unclear (blank).

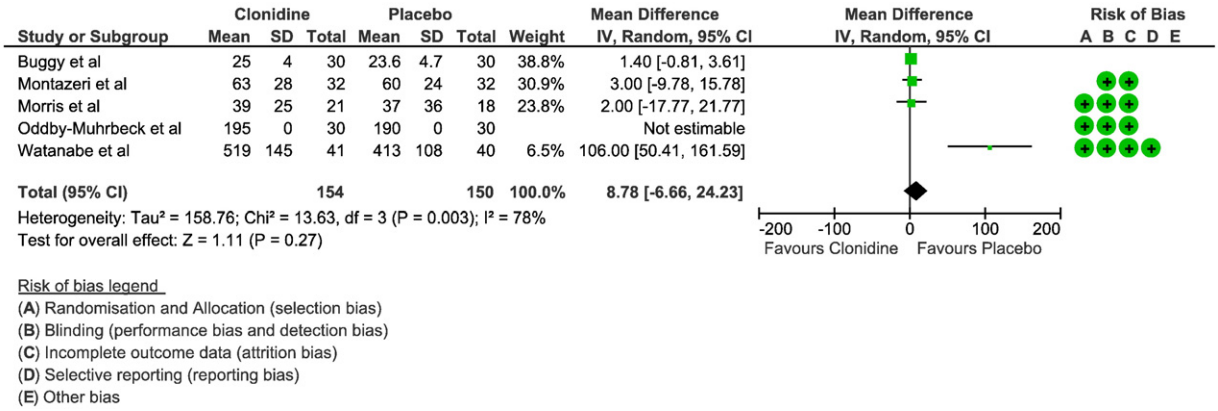

Fig. 9. Forest plot for recovery time difference, in randomized-controlled trials comparing clonidine vs placebo. For risks of biases: + = low risk; − = high risk; blank = unclear.

biodisponibility of clonidine by mouth and the fact that most of the studies using oral clonidine administered it 1 to 2 h before surgery (to reach a peak plasma concentration at the induction of anesthesia [4]), it seemed logical to pool studies focusing on PO and IV clonidine. It is worth too to mention that postoperative pain as PONV are affected by the type of surgery.

5. Conclusions

In conclusion, these systematic review and meta-analyses of 57 trials shows that clonidine improves pain control, reduces PONV, improves hemodynamic and sympathetic stabilities, with no adverse consequences on renal function or awakening time, but does not influence cardiac outcome in the general population after non-cardiac surgery. Nevertheless, given the high heterogeneity between the studies, this does not exclude different results in patient subgroups or specific procedures. Further research may focus on the best candidates (patients) for clonidine indications, and on the way to adapt the dose to the patients and the procedure.

Authors' contributions

MCSM and PF designed the study. MCSM collected, selected with PF, and both performed the qualitative analyses. PF performed the quantitative analyses. MCSM, MDK and PF performed the interpretation, contributed to the manuscript preparation and approved the final version.

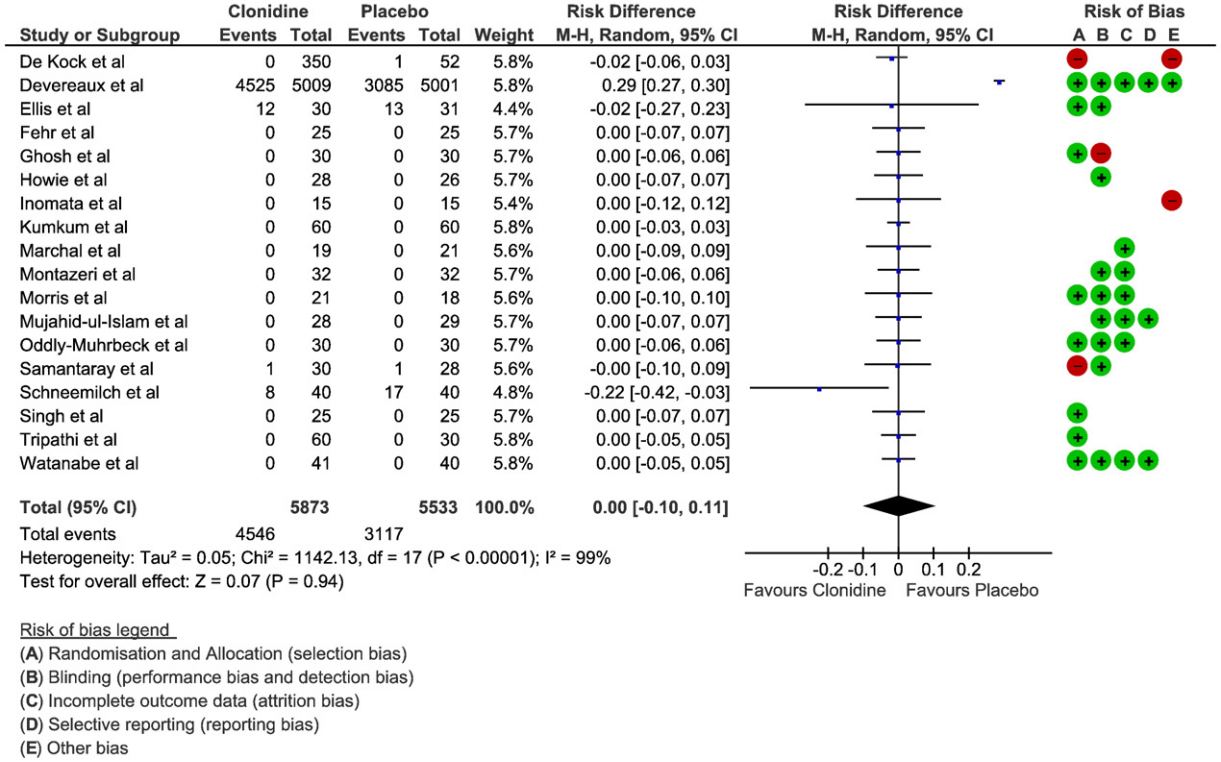

Fig. 10. Forest plot for adverse events occurrence rates, in randomized-controlled trials comparing clonidine vs placebo. For risks of biases: + = low risk; − = high risk; blank = unclear.

Conflict of interest

None.

Funding source

No external funding source.

Appendix A

A.1. Risk of bias details

Sequence generation, allocation concealment, blinding of participants and personnel, incomplete data outcome, selective output reporting and any potential sources of bias were analyzed. Funnel plots were used to analyze a potential publication bias and no evidence of such bias was founded.

A.2. Data extraction details

For postoperative analgesia we extracted the time to first analgesia request (TAR) or time to first analgesic injection (FAI), visual analog scale (VAS) at 12, 24 and 48 h, and analgesic consumption at 24, 36 and 48 h.

For postoperative nausea and vomiting (PONV), we extracted the incidence of PONV at 24 h, PONV free and antiemetic rescue at 24 h.

For intraoperative bleeding we extracted blood loss scores, surgeon satisfaction and blood loss volumes.

For induction time, we extracted the induction time whichever the type of anesthetic induction.

For hemodynamic stability, we separated the data concerning hemodynamic response to tracheal intubation from these concerning hemodynamic stability during pneumoperitoin induction for laparoscopic surgery (heart rate (HR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and mean arterial pressure (MAP) before and 1, 2, 3, 4, 5, 7, 10 and 15 min after the intubation; and HR, SAP, DAP and MAP before and after the induction, before and 1, 5, 10, 15, 30 and 60 min after the insufflation, after the CO_2 release and after the tracheal extubation).

For hormonal stability and catecholamine secretion, we extracted epinephrine, norepinephrine, cortisol and glucose levels.

For oxygen consumption, we extracted preoperative, preoperative and postoperative VO_2.

For kidney function, we extracted 24 h urine output, urine potassium and sodium, urine osmolality and plasma renin activity.

For anesthetics-sparing effect, we extracted the anesthetics requirements.

For postoperative shivering, we extracted the incidence, severity and duration of shivering, the core temperature and Thermal Comfort Score (TCS - a value of 10 indicated extreme heat discomfort and a value of 1 indicated extreme cold discomfort). Data were separated whether clonidine was studied as a prophylactic intervention or a treatment.

For anxiolysis and sedative effect, we extracted the anxiety and sedation scores as reported (VAS for anxiety ranged from 0 “not anxious at all” to 100 mm “most anxious I can imagine”, VAS for sedation ranged 0 “not sleepy at all” to 100 mm “extremely sleepy”, Ramsay sedation scale*, Observer's Assessment of Alertness/Sedation – OAAS, sedation score ranged 1 “wide awake”, 2 “sleeping comfortably but responding verbal commands”, 3 “deep sleep but arousable”, 4 “deep sleep but not arousable” and anxiety score ranged 0 “quiet and comfortable”, 1 “uneasy”, 2 “worried and anxious”, 3 “very worried or very upset”, 4 frightened or terrified).

For recovery time, we extracted time in recovery room, time to eyes opening, time for name declaration, time to date of birth declaration, time to age declaration, time to response to verbal commands and time to complete arousal.

For satisfaction, we extracted level of satisfaction as reported in original trials (1–4 scale ranged 1 “totally dissatisfied”, 2 “moderately dissatisfied”, 3 “reasonably satisfied” and 4 “totally satisfied”).

For cardiac protection we extracted all the patient's outcomes.

References

[1] Devereaux PJ, Sessler DI, Leslie K, Kurz A, Mrkobrada M, Alonso-Coello P, et al. POISE-2 investigators. Clonidine in patients undergoing noncardiac surgery. N Engl J Med 2014 Apr 17;370(16):1504–13.
[2] Aitkenhead AR, Rowbotham DJ, Smith G. Drugs acting on the cardiovascular and autonomic nervous system. Textbook of anaesthesia. 4th ed. Edinburgh: Churchill Livingstone; 2001. p. 65–100.
[3] Davies DS, Wing LHM, Reid JL, Neil E, Tippett P, Dollery CT. Pharmacokinetics and concentration-effect relationships of intravenous and oral clonidine. Clin Pharmacol Ther 1977;21:593–601.
[4] Lowenthal DT, Matzek KM, MacGregor TR. Clinical pharmacokinetics of clonidine. Clin Pharmacokinet 1988;14:287–310.
[5] Hayashi Y, Maze M. Alpha 2 adrenoceptor agonists and anaesthesia. Br J Anaesth 1993;71:108–18.
[6] Urrútia G, Bonfill X. PRISMA declaration: a proposal to improve the publication of systematic reviews and meta-analyses. Med Clin (Barc) 2010 Oct 9;135(11):507–11.
[7] Taheri A, Javadimanesh MA, Ashraf H. The effect of oral clonidine premedication on nausea and vomiting after ear surgery. Middle East J Anaesthesiol 2010 Jun;20(5):691–4.
[8] Ganter MT, Hofer CK, Spahn DR, Bruggisser M, Bombeli T, Seifert B, et al. The effect of clonidine on perioperative blood coagulation. J Clin Anesth 2005 Sep;17(6):456–62.
[9] Taghipour Anvari Z, Afshar-Fereydouniyan N, Imani F, Sakhaei M, Alijani B, Mohseni M. Effect of clonidine premedication on blood loss in spine surgery. Anesth Pain Med 2012 Spring;1(4):252–6.
[10] Szpalski M, Gunzburg R, Sztern B. An overview of blood-sparing techniques used in spine surgery during the perioperative period. Eur Spine J 2004;13(Suppl. 1):18–27.
[11] Watanabe T, Inagaki Y, Ishibe Y. Clonidine premedication effects on inhaled induction with sevoflurane in adults: a prospective, double-blind, randomized study. Acta Anaesthesiol Scand 2006 Feb;50(2):180–7.
[12] Singhal SK, Kaur K, Arora P. Oral clonidine versus gabapentin as premedicant for obtunding hemodynamic response to laryngoscopy and tracheal intubation. Saudi J Anaesth 2014 Apr;8(2):172–7.
[13] Reid LC, Brace DE. Irritation of the respiratory tract and its reflex effect upon the heart. Surg Gynecol Obstet 1940;70:157–62.
[14] King BD, Harris Jr LC, Greifenstein FE, Elder Jr JD, Dripps RD. Reflex circulatory responses to direct laryngoscopy and tracheal intubation performed during general anesthesia. Anesthesiology 1951;12:556–66.
[15] Matovic E, Hasukic Ljuca F, Halilovic H. Quality of life in patient after laparoscopic and open cholecystectomy. Mediev Archaeol 2012;66:97–100.
[16] Ellis JE, Drijvers G, Pedlow S, Laff SP, Sorrentino MJ, Foss JF, et al. Premedication with oral and transdermal clonidine provides safe and efficacious postoperative sympatholysis. Anesth Analg 1994 Dec;79(6):1133–40.
[17] Eisinger H, Weichel T, Lindner KH, Grünert A, Ahnefeld FW. Effects of norepinephrine, epinephrine and dopamine infusions on oxygen consumption in volunteers. Crit Care Med 1993;21:1502–8.
[18] Vallès J, Samsó E, Vilar X, Gallart L, Puig MM. Pharmacy savings generated by preoperative administration of clonidine. J Clin Anesth 1998 Feb;10(1):36–40.
[19] Buggy D, Higgins P, Moran C, O'Donovan F, McCarroll M. Clonidine at induction reduces shivering after general anaesthesia. Can J Anaesth 1997 Mar;44(3):263–7.
[20] Devereaux PJ, Chan M, Eikelboom J. Major vascular complication in patients undergoing non-cardiac surgery: magnitude of the problem, risk protection, surveillance, and prevention. In: Yusuf S, Cairns JA, Camm AJ, Fallen EL, Gersh BJ, editors. Evidence-based cardiology. 3rd ed. Chichester, England: Wiley-Blackwell; 2010. p. 47–62.
[21] Ohata H, Iida H, Watanabe Y, Dohi S. Hemodynamic responses induced by dopamine and dobutamine in anesthetized patients premedicated with clonidine. Anest Analg 1999 Oct;89(4):843–8.
[22] Filos KS, Patroni O, Goudas LC, Bosas O, Kassaras A, Gartaganis S. A dose-response study of orally administered clonidine as premedication in the elderly: evaluating hemodynamic safety. Anesth Analg 1993 Dec;77(6):1185–92.
[23] Maruyama K, Takeda S, Hongo T, Kobayashi N, Kim C, Ogawa R. Oral clonidine premedication exacerbates hypotension following tourniquet deflation by inhibiting noradrenaline release. J Nippon Med Sch 2004 Feb;71(1):44–50.
[24] Samantaray A, Rao MH, Chandra A. The effect on post-operative pain of intravenous clonidine given before induction of anaesthesia. Indian J Anaesth 2012;56(4):359–64.
[25] Singh S, Arora K. Effect of oral clonidine premedication on perioperative haemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy. Indian J Anaesth 2011;55(1):26–30.
[26] Caumo W, Levandovski R, Hidalgo MP. Preoperative anxiolytic effect of melatonin and clonidine on postoperative pain and morphine consumption in patients undergoing abdominal hysterectomy: a double-blind, randomized, placebo-controlled study. J Pain 2009 Jan;10(1):100–8.

[27] Yu HP, Hseu SS, Yien HW, Teng YH, Chan KH. Oral clonidine premedication preserves heart rate variability for patients undergoing laparoscopic cholecystectomy. Acta Anaesthesiol Scand 2003 Feb;47(2):185–90.
[28] Marchal JM, Gómez-Luque A, Martos-Crespo F, Sánchez De La Cuesta F, Martínez-López MC, Delgado-Martinez AD. Clonidine decreases intraoperative bleeding in middle ear microsurgery. Acta Anaesthesiol Scand 2001 May;45(5):627–33.
[29] Dimou P, Paraskeva A, Papilas K, Fassoulaki A. Transdermal clonidine: does it affect pain after abdominal hysterectomy? Acta Anaesthesiol Belg 2003;54(3):227–32.
[30] Park J, Forrest J, Kolesar R, Bhola D, Beattie S, Chu C. Oral clonidine reduces postoperative PCA morphine requirements. Can J Anaesth 1996 Sep;43(9):900–6.
[31] De Kock MF, Pichon G, Scholtes JL. Intraoperative clonidine enhances postoperative morphine patient-controlled analgesia. Can J Anaesth 1992 Jul;39(6):537–44.
[32] Jeffs SA, Hall JE, Morris S. Comparison of morphine alone with morphine plus clonidine for postoperative patient-controlled analgesia. Br J Anaesth 2002 Sep;89(3):424–7.
[33] Horn EP, Werner C, Sessler DI, Steinfath M, Schulte am Esch J. Late intraoperative clonidine administration prevents postanesthetic shivering after total intravenous or volatile anesthesia. Anesth Analg 1997 Mar;84(3):613–7.
[34] Yadav G, Pratihary BN, Jain G, Paswan AK, Mishra LD. A prospective, randomized, double blind and placebo-control study comparing the additive effect of oral midazolam and clonidine for postoperative nausea and vomiting prophylaxis in granisetron premedicated patients undergoing laparoscopic cholecystectomy. J Anaesthesiol Clin Pharmacol 2013 Jan;29(1):61–5.
[35] Taheri A, Javadimanesh MA, Ashraf H. The effect of oral clonidine premedication on nausea and vomiting after ear surgery. Middle East J Anaesthesiol 2010 Jun;20(5):691–4.
[36] Oddby-Muhrbeck E, Eksborg S, Bergendahl HT, Muhrbeck O, Lönnqvist PA. Effects of clonidine on postoperative nausea and vomiting in breast cancer surgery. Anesthesiology 2002 May;96(5):1109–14.
[37] Mohseni M, Ebneshahidi A. The effect of oral clonidine premedication on blood loss and the quality of the surgical field during endoscopic sinus surgery: a placebo-controlled clinical trial. J Anesth 2011 Aug;25(4):614–7.
[38] Inomata S, Yaguchi Y, Toyooka H. The effects of clonidine premedication on sevoflurane requirements and anesthetic induction time. Anesth Analg 1999 Jul;89(1):204–8.
[39] Mujahid-ul-Islam, Ahmad I, Rafique K, Kamal R, Abbas F. Oral clonidine for attenuation of haemodynamic response to laryngoscopy and endotracheal intubation in known hypertensive patients. J Ayub Med Coll Abbottabad 2012 Jul–Dec;24(3–4):174–6.
[40] Montazeri K, Kashefi P, Honarmand A, Safavi M, Hirmanpour A. Attenuation of the pressor response to direct laryngoscopy and tracheal Intubation: oral clonidine vs. oral gabapentin premedication. J Res Med Sci 2011 Mar;16(Suppl. 1):S377–86.
[41] Sameenakousar Mahesh, Srinivasan KV. Comparison of fentanyl and clonidine for attenuation of the haemodynamic response to laryngoscopy and endotracheal intubation. J Clin Diagn Res 2013 Jan;7(1):106–11.
[42] Talebi H, Nourozi A, Fateh S, Mohammadzadeh A, Eghtesadi-Araghi P, Jabbari S, et al. Effects of oral clonidine premedication on haemodynamic response to laryngoscopy and tracheal intubation: a clinical trial. Pak J Biol Sci 2010 Dec 1;13(23):1146–50.
[43] Doak GJ, Duke PC. Oral clonidine premedication attenuates the haemodynamic effects associated with ketamine anaesthetic induction in humans. Can J Anaesth 1993 Jul;40(7):612–8.
[44] Gupta K, Sharma D, Gupta PK. Oral premedication with pregabalin or clonidine for hemodynamic stability during laryngoscopy and laparoscopic cholecystectomy: a comparative evaluation. Saudi J Anaesth 2011 Apr;5(2):179–84.
[45] Tripathi DC, Shah KS, Dubey SR, Doshi SM, Raval PV. Hemodynamic stress response during laparoscopic cholecystectomy: effect of two different doses of intravenous clonidine premedication. J Anaesthesiol Clin Pharmacol 2011 Oct;27(4):475–80.
[46] Kalra NK, Verma A, Agarwal A, Pandey H. Comparative study of intravenously administered clonidine and magnesium sulfate on hemodynamic responses during laparoscopic cholecystectomy. J Anaesthesiol Clin Pharmacol 2011 Jul;27(3):344–8.
[47] Kalajdzija M, Cero I, Prnjavorac B, Ljuca S. Influence of clonidine on the chemodynamic stability and stress response in the course of surgery on general anesthesia. Med Arh 2011;65(4):210–2.
[48] Schneemilch CE, Bachmann H, Ulrich A, Elwert R, Halloul Z, Hachenberg T. Clonidine decreases stress response in patients undergoing carotid endarterectomy under regional anesthesia: a prospective, randomized, double-blinded, placebo-controlled study. Anesth Analg 2006 Aug;103(2):297–302.
[49] Hahm TS, Cho HS, Lee KH, Chung IS, Kim JA, Kim MH. Clonidine premedication prevents preoperative hypokalemia. J Clin Anesth 2002 Feb;14(1):6–9.
[50] Howie MB, Hiestand DC, Jopling MW, Romanelli VA, Kelly WB, McSweeney TD. Effect of oral clonidine premedication on anesthetic requirement, hormonal response, hemodynamics, and recovery in coronary artery bypass graft surgery patients. J Clin Anesth 1996 Jun;8(4):263–72.
[51] Taittonen MT, Kirvelä OA, Aantaa R, Kanto JH. The effect of clonidine or midazolam premedication on perioperative responses during ketamine anesthesia. Anesth Analg 1998 Jul;87(1):161–7.
[52] Taittonen MT, Kirvelä OA, Aantaa R, Kanto JH. Effect of clonidine and dexmedetomidine premedication on perioperative oxygen consumption and haemodynamic state. Br J Anaesth 1997 Apr;78(4):400–6.
[53] Von Montigny S, Laterre PF, Vanderelst P, De Kock M. The effects of intraoperative intravenous clonidine on gastric intramucosal PCO2. Anesth Analg 1998 Sep;87(3):686–90.
[54] Vahabi S, Heidari M, Kazemi AH, Birjandi M, Iran-Pour E. Assessment of clonidine effect as premedicative drug on kidney function. J Pak Med Assoc 2010 Jul;60(7):570–2.
[55] Laisalmi M, Koivusalo AM, Valta P, Tikkanen I, Lindgren L. Clonidine provides opioid-sparing effect, stable hemodynamics, and renal integrity during laparoscopic cholecystectomy. Surg Endosc 2001 Nov;15(11):1331–5 [Epub 2001 Aug 16].
[56] Hamaya Y, Nishikawa T, Dohi S. Diuretic effect of clonidine during isoflurane, nitrous oxide, and oxygen anesthesia. Anesthesiology 1994 Oct;81(4):811–9.
[57] Moghadam MJ, Ommi D, Mirkheshti A, Shadnoush M, Dabbagh A. The effect of pretreatment with clonidine on propofol consumption in opium abuser and non-abuser patients undergoing elective leg surgery. J Res Med Sci 2012 Aug;17(8):728–31.
[58] Ghosh I, Bithal PK, Dash HH, Chaturvedi A, Prabhakar H. Both clonidine and metoprolol modify anesthetic depth indicators and reduce intraoperative propofol requirement. J Anesth 2008;22(2):131–4.
[59] Morris J, Acheson M, Reeves M, Myles PS. Effect of clonidine pre-medication on propofol requirements during lower extremity vascular surgery: a randomized controlled trial. Br J Anaesth 2005 Aug;95(2):183–8.
[60] Fehr SB, Zalunardo MP, Seifert B, Rentsch KM, Rohling RG, Pasch T, et al. Clonidine decreases propofol requirements during anaesthesia: effect on bispectral index. Br J Anaesth 2001;86(5):627–32.
[61] Goyagi T, Tanaka M. Nishikawa T oral clonidine premedication reduces propofol requirement for laryngeal mask airway insertion. Can J Anaesth 2000 Jul;47(7):627–30.
[62] Goyagi T, Tanaka M, Nishikawa T. Oral clonidine premedication reduces induction dose and prolongs awakening time from propofol-nitrous oxide anesthesia. Can J Anaesth 1999 Sep;46(9):894–6.
[63] Imai Y, Mammoto T, Murakami K, Kita T, Sakai T, Kagawa K, et al. The effects of preanesthetic oral clonidine on total requirement of propofol for general anesthesia. J Clin Anesth 1998 Dec;10(8):660–5.
[64] Katoh T, Ikeda K. The effect of clonidine on sevoflurane requirements for anaesthesia and hypnosis. Anaesthesia 1997 Apr;52(4):377–81.
[65] Jabbary Moghaddam M, Ommi D, Mirkheshti A, Dabbagh A, Memary E, Sadeghi A, et al. Effects of clonidine premedication upon postoperative shivering and recovery time in patients with and without opium addiction after elective leg fracture surgeries. Anesth Pain 2013;2(3):107–10.
[66] Vanderstappen I, Vandermeersch E, Vanacker B, Mattheussen M, Herijgers P, Van Aken H. The effect of prophylactic clonidine on postoperative shivering. A large prospective double-blind study. Anaesthesia 1996 Apr;51(4):351–5.
[67] Sia S. I.V. clonidine prevents post-extradural shivering. Br J Anaesth 1998 Aug;81(2):145–6.
[68] Schwarzkopf KR, Hoff H, Hartmann M, Fritz HG. A comparison between meperidine, clonidine and urapidil in the treatment of postanesthetic shivering. Anesth Analg 2001 Jan;92(1):257–60.
[69] Shukla U, Malhotra K, Prabhakar T. A comparative study of the effect of clonidine and tramadol on post-spinal anaesthesia shivering. Indian J Anaesth 2011 May;55(3):242–6.
[70] Rocha AP, Barros GA, Nascimento Jdos S, Santos KP, Vasconcelos LM, Castro PA. Sedation with sufentanil and clonidine in patients undergoing heart catheterization. Arq Bras Cardiol 2011 Mar;96(3):21926.
[71] Singh M, Choudhury A, Kaur M, Liddle D, Verghese M, Balakrishnan I. The comparative evaluation of intravenous with intramuscular clonidine for suppression of hemodynamic changes in laparoscopic cholecystectomy. Saudi J Anaesth 2013 Apr;7(2):181–6.
[72] De Kock M, Versailles H, Colinet B, Karthaeuser R, Scholtes JL. Epidemiology of the adverse hemodynamic events occurring during “clonidine anesthesia”: a prospective open trial of intraoperative intravenous clonidine. J Clin Anesth 1995 Aug;7(5):403–10.