Laparoscopic appendectomy in adult patients: locoregional or general anesthesia? A meta-analysis

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Background: Laparoscopic visceral resections under locoregional anesthesia are still debated. Aim of this study is to evaluate feasibility and effectiveness of regional anesthesia for laparoscopic appendectomy in adult patients.

Methods: A PubMed-MEDLINE Embase, Cochrane Database and Google Scholar systematic review was carried out. Both primary and secondary endpoints were investigated. Relative risk for each item was pooled and no bias according to Cochrane Collaboration's tool and funnel plot asymmetry test were found.

Results: Four randomized controlled trials, including 280 patients, were enrolled. Regional anesthesia increased the risk of intraoperative arterial hypotension (RR: 8.00, P=0.048) without significant correlation with bradycardia (RR: 3.00, P=0.050). On the other hand, locoregional techniques statistically reduced the incidence of shoulder pain (RR: 0.35, P=0.023) and postoperative nausea and vomiting (RR: 0.18, P=0.024). Transient urinary retention was higher in this cohort without clinical relevance (RR: 11.00, P=0.103), but these patients experienced a substantial reduction of postoperative pain in the immediate perioperative period (RA-VAS *vs.* GA-VAS: 1.17±0.39 *vs.* 4.83±0.70, P<0.001). Although hospital stay was similar (P=0.001), both time to mobilization and time to peristalsis resumption favoured the interventional brace (RA-LA *vs.* GA-LA: 11.75±1.75 *vs.* 16.60±2.70; P<0.001 and RA-LA *vs.* GA-LA: 6.95±1.50 *vs.* 7.85±2.35; P=0.011).

Conclusions: Locoregional anesthesia laparoscopic appendectomies in adult patients are effective and safe, as being a valid alternative to general anesthesia not only for high-risk patients.

Keywords: Laparoscopic appendectomy; locoregional anesthesia; general anesthesia; outcome

Introduction

Acute appendicitis is one of the most common abdominal surgical emergencies worldwide (1), whose standard of care approach is nowadays laparoscopically (2) despite its low to moderate quality of evidences. However, laparoscopic appendectomy (LA) shows some advantages over open surgery, like less wound infections, less postoperative pain, shorter hospital stay and recovery periods for daily activities (3).

The gradual shift towards minimally invasive surgical strategies has dramatically influenced both practices and

techniques of anesthesia by propelling innovations and initiatives for newer and safer protocols aiming to early recovery and ambulation (4). Notwithstanding some efforts, laparoscopic surgeries are generally managed under general anesthesia (GA), as a regional one being traditionally widely discouraged due to some concerns about intraoperative discomfort and side effects imbibing empiricism and lack of evidences (5,6). In this regard, although several studies suggest regional anesthesia (RA) may be a safe alternative to GA for laparoscopic surgery (7,8), many aspects remain unsolved, such as the risk of intraoperative hypotension, ventilatory impairment, shoulder pain due to diaphragmatic irritation, patients' discomfort with subsequent increased surgical time (9). Basing on these discussed and controversial aspects, the feasibility and safety of regional anesthesia in laparoscopic appendectomy had been investigated through a systematic review and meta-analysis by evaluating the pooled intraoperative and postoperative patients' outcome.

Methods

Study design

A PubMed-MEDLINE Embase, Cochrane Database and Google Scholar literature research was carried out by three investigators from the authors' group in order to identify relevant data published from Jan 01, 2000 to Oct 31, 2019 on the attempt of a homogeneous report among articles according to availability of techniques and validation of both surgical and anesthesiological expertises. The Boolean function, according the medical subject heading (MeSH) item, was as follows: (((((((laparoscopic) OR minimally invasive) AND appendectomy) AND general anesthesia) OR regional anesthesia) OR epidural anesthesia) OR subarachnoid anesthesia) AND ("2000/01/01"(Date - Publication): "2019/10/31"(Date - Publication)). Additional manual selection process of unlisted references from unindexed sources (Google Scholar) was included via a two-step researches run on November 03, 2019 and November 15, 2019, respectively. All selected potentially relevant papers were reviewed and checked by a four-phase approach (source reliability, title, abstract and critical full-text evaluation) according the following inclusion criteria: (I) both elective and emergent laparoscopic or minimally invasive appendectomy in adult patients; (II) a 1:1 allocated cohort analysis between general and regional anesthetic protocols; (III) a clearly definition of both inclusion and exclusion adopted criteria; (IV) an exhaustive

description of surgical techniques (number and sites of lap ports, pneumoperitoneum pressure, medical devices adoption); (V) a detailed explanation of anesthesiological protocols (both for general and regional anesthesia); (VI) a complete description of patients' outcome according to both intraoperative and postoperative side effects as far as postoperative pain [assessed via a Visual Analogue Scale (VAS) scoring system]; (VII) articles written only in English. Only prospective randomized-controlled trials (RCTs) were included, as the poor statistical relevance of case series, case reports and review articles. Trials comparing different protocols or drug administration in the same cohort were excluded as far as reports about pediatric cases. Subsequent data extraction from eligible articles was carried out by three independent reviewers to collect the following informations: authors' detail, year of publication, country of publication, type of study, the period of patients' enrollment, study inclusion and exclusion criteria (if applicable), surgical and anesthetic technique (*Table 1*).

Endpoints

In order to evaluate both safety and feasibility of regional anesthesia in laparoscopic appendectomy, several primary endpoints were analysed:

(I) Intraoperative arterial hypotension;
(II) Intraoperative bradycardia;
(III) Postoperative shoulder pain;
(IV) Postoperative nausea or vomiting;
(V) Postoperative bladder retention;
(VI) Postoperative pain.

Secondary endpoint included the evaluation of hospital stay, postoperative mobilization and small bowel sound resumption.

Statistical analysis

The meta-analysis was conducted with Microsoft Excel 2016 (Microsoft®, Redmond, USA) and with IBM SPSS version 20.0 (IBM®, Segrate MI, Italy). Data were reported as absolute numbers (N), percentages (%), means, standard deviations (SDs) with their relative 95% confidence interval (95% CI). Statistical differences or correlations between cohorts were evaluated with paired t-test both for categorical and continuous variables. Standard errors (S.E.) and differences (Df) were also reported. For both primary and secondary endpoints, a summarized 2×2 contingency plot (exposed good event x exposed bad event/ control

Table 1 Eligible articles: study designs, indications, surgical and anesthesiological protocols

Author	Year	Country	Type of study	Period	Enrolled patients	Inclusion criteria	Surgical indications	Surgical techniques	Anesthesiological protocols
Erdem MV et al. (10)	2018	Turkey	RCT	2015	50	Adult ASA < III patients, no allergic diathesis, no history of abdominal surgery and pregnancy	Acute appendicitis, carcinoid tumors	Three-port Verres laparoscopy. Trendelenburg position. Ultrasonic-based dissection and endoloop stump closure without any postoperative drainage	No premedication. GA group: propofol 2–2.5 mg/kg and fentanyl 1 µg/kg (induction); Rocuronium 0.6 mg/kg; VCV (tV: 6–8ml/kg); Sevoflurane 1.5–2% with an oxygen-air mixture (FiO$_2$ =0.4) for maintenance. Neostigmine 2–2.5 mg and atropine 1 mg RA group (combined spinal/epidural anesthesia); hyperbaric bupivacaine 0.5% 10 mg + fentanyl 10 µg L3–L4 injection (spinal); bupivacaine 0.5% 10ml, fentanyl 25 µg and isotonic saline 5 mL (epidural). Level of sensorial nerve block: T4
Kumar S et al. (11)	2019	India	RCT	2016	100	Adult ASA < III patients, normal coagulation profile	Acute appendicitis	NR	NR
Mehanna AMAM et al. (12)	2017	Egypt	RCT	2015–2016	80	Adult ASA < III patients, BMI < 30 kg/m^2	Acute appendicitis	Three-port open laparoscopy. 12 mmHg CO$_2$ pneumoperitoneum. No trendelenburg position. Ultrasonic-based dissection and endoloop stump closure	GA group: propofol 2.5 mg/kg, fentanyl 1 µg/kg (induction); Atracurium besylate (0.5 mg/gL); Sevoflurane 2–3% with a 0.5 FiO$_2$ oxygen-air mixture RA group: hyperbaric bupivacaine 15 mg + fentanyl 25 µg. Level of sensorial nerve block: T4
Shrivastava D et al. (13)	2019	India	RCT	2016–2018	50	Adult ASA < III patients, BMI < 30 kg/m^2	Acute appendicitis	NR	GA group: propofol 2.5 mg/kg, fentanyl 1 µg/kg (induction); Succinyl chlorine 1.5 mg/kg. Atracurium besylate (0.5 mg/gL); Sevoflurane 2–3% with a 0.5 FiO$_2$ oxygen-air mixture RA group: hyperbaric bupivacaine 15 mg + fentanyl 25 µg. Level of sensorial nerve block: T4

RCT, randomized-controlled trial (1:1 allocation); ASA, American Society of Anesthesiologists Classification; VCV, volume-controlled ventilation; NR, not reported.

good event x control bad event) was derived. Relative risk, as defined as the ratio of the probability of an event occurs in an exposed cohort versus the probability the same event occurs in the control one, was calculated according to the formula: $RR = [a/(a+b)]/[c/(c+d)]$. The overall test effect for each item was assessed according to both z-effect function and P value derivation. A value <0.05 for both was considered significant. RR Forest plots were derived for summarized visual evaluation. A RR threshold >1.00 was considered significant and thus suggesting non-negligible positive or negative effects.

Results

Data extraction process

According the MeSH terms Boolean function and throughout the adoption of the PRISMA © flow diagram guidelines (http://www.prisma-statement.org/), 57 potentially relevant articles were identified by four investigators. Further, 4 unindexed papers were included from web research for a total of 61 eligible for analysis. Thereafter, 39 were removed basing upon title and ulterior 10 after their abstract evaluation. A second step full-text analysis was brought out for the 12 remaining articles and only four were included for meta-analysis (10-13). In particular: (I) four papers were rejected due to their study design incompatibility (case series reports); (II) one article due to cohort incompatibility (pediatric population); (III) one article due to the lack of exhaustive data and (IV) two articles due to the availability of only abstracts. At the end of this process, 280 1:1 randomized allocated patients (140 RA-LA vs. 140 GA-LA) were enrolled (*Figure 1*).

Primary quantitative and qualitative evaluation

Preliminarily, a quantitative evaluation of the eligible articles was carried out in order to evaluate the presence of any selection bias through an asymmetry funnel plotting test which confirmed the heterogeneity of the enrolled population (S.E.=0.61, 95% CI: 0.41–0.77; P=0.296) (*Figure 2*). Concerning with qualitative analysis, investigators referred to the Cochrane Collaboration's tool (14), as reported in *Figure 3*. Although no critical issues were found in the design of the studies (randomization, allocation, double-blind analysis), sources of bias were highlighted in patients' outcome. In particular, one study (11) presented an incomplete description of intraoperative side effects and

resorted to an arbitrary and inexhaustible assessment of the pain, resulting in a non-negligible risk of selective reporting. Two further articles (12,13), on the other hand, lacked secondary details about the demographic characteristics of the enrolled populations.

Intra- and postoperative events: primary endpoints

Arterial hypotension

Episodes of intraoperative arterial hypotension were reported in all the elected article, enrolling 280 patients (RA-LA vs. GA-LA: 140 vs. 140). At the weighted-pooled analysis, no significant cumulative effects were found among included studies (17.86% vs. 35.71% vs. 28.57% vs. 17.86%; 95% CI: –11.47–29.25, Df: 10.71, P=0.332). With an incidence of significant decrease in blood pressure (σ>2 SD) of 5.71% and 0.71% respectively, a significant difference between cohorts was found (RR: 8.00, 95% CI: 1.01–63.12, z-effect: 1.97, P=0.048), suggesting an increased risk of intraoperative hypotension events in patients undergoing awake laparoscopic surgery (*Table 2*) (*Figure 4A*).

Bradycardia

The occurrence of bradycardic episodes was investigated in all articles, enrolling 280 patients (RA-LA vs. GA-LA: 140 vs. 140). At the weighted-pooled analysis, no significant cumulative effects were found among included studies (17.86% vs. 35.71% vs. 28.57% vs. 17.86%; 95% CI: –11.47–29.25, Df: 10.71, P=0.332). With a rough incidence of 0.71% and 0%, the Forrest analysis revealed no significant correlations between the anesthetic technique and the occurrence of bradycardic episodes, although in the presence of a risk value consistently above the influence threshold (RR: 3.00, 95% CI: 0.12–73.02, z-effect: 0.67, P=0.500) (*Table 2*) (*Figure 4B*).

Shoulder pain

Shoulder pain was described in all the reports. At the weighted-pooled analysis, no significant cumulative effects were found among included studies (17.86% vs. 35.71% vs. 28.57% vs. 17.86%; 95% CI: –11.47–29.25, Df: 10.71, P=0.332). With an incidence of 2.75% and 6.37% between cohorts, patients undergoing RA-LA experienced a substantial reduction of painful episodes without any significant exposure risk than their GA counterparts (RR: 0.35, 95% CI: 0.14–0.87, z-effect: 2.27, P=0.023) (*Table 2*) (*Figure 4C*).
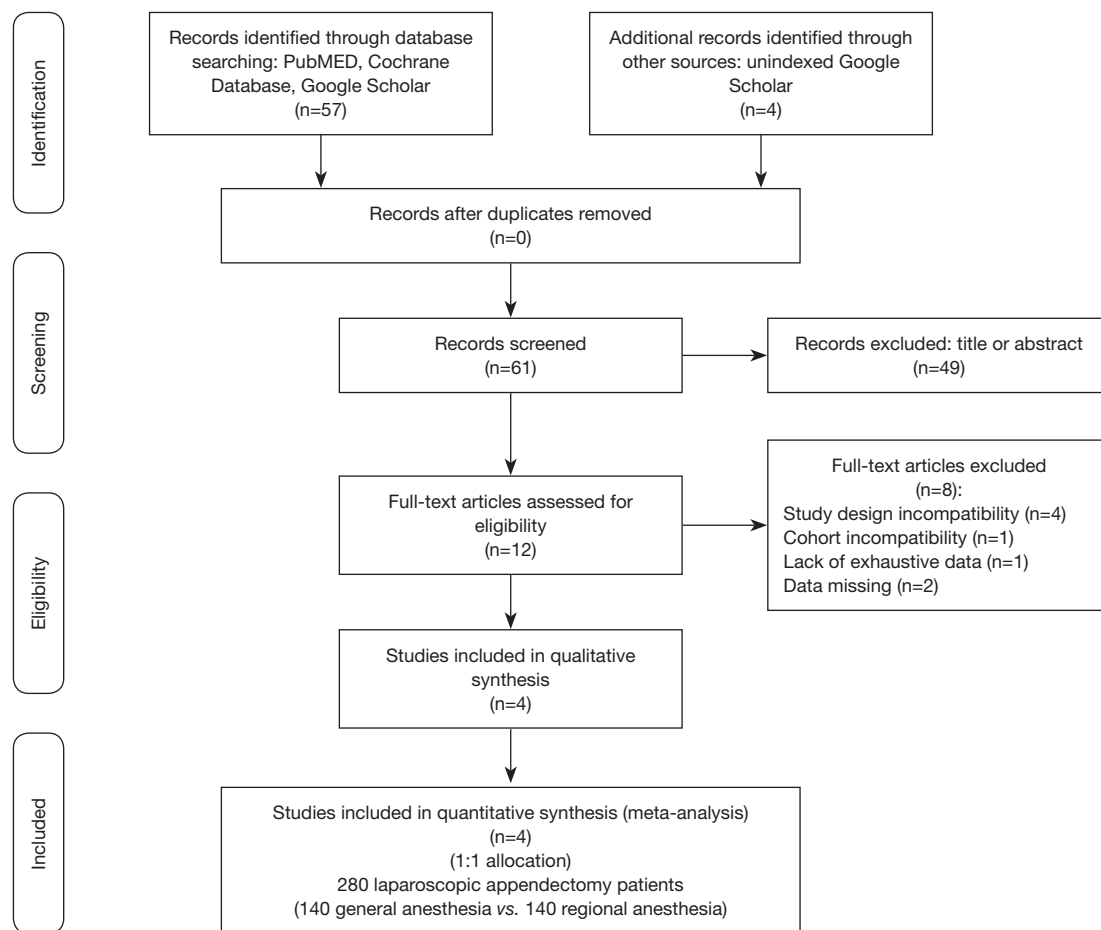
Figure 1 PRISMA© Eligibility process flow diagram.

Postoperative nausea and vomiting (PONV)

The eventuality of PONV episodes was evaluated in all the RCTs elected. At the weighted-pooled analysis, no significant cumulative effects were found among included studies (17.86% *vs.* 35.71% *vs.* 28.57% *vs.* 17.86%; 95% CI: −11.47–29.25, Df: 10.71, P=0.332) and a PONV incidence of 0.81% and 4.37% was reported. Locoregional anesthesia techniques applied to the laparoscopic approach significantly preserved patients from the aforementioned postoperative side effect (RR: 0.18, 95% CI: 0.41–0.80, z-effect: 2.24, P=0.024) (*Table 2*) (*Figure 4D*).

Urinary retention

Postoperative urinary retention (POUR) was evaluated in all the RCTs elected. At the weighted-pooled analysis, no significant cumulative effects were found among included studies (17.86% *vs.* 35.71% *vs.* 28.57% *vs.* 17.86%; 95% CI: −11.47–29.25, Df: 10.71, P=0.332) and a POUR incidence

of 3.57% and 0% between cohorts was reported. Although RA-LA patients were significantly exposed to an augmented risk of micturition dyssynergism (RR: 11.00), no significant differences were reported (95% CI: 0.61–197.07, z-effect: 1.63; P=0.103) (*Table 2*) (*Figure 4E*).

Postoperative pain (visual analogue assessment)

Postoperative pain was assessed by adopting the analogue visual scale, through repeated interviews in the immediate awakening (VAS 0), six hours (VAS 6) and twelve hours after surgery (VAS 12). At each survey, a statistically significant difference between the two groups was noted, consistently favouring a locoregional approach (VAS 0 *vs.* VAS 6 *vs.* VAS 12: S.E.=0.07, t=−54.59, P<0.001; S.E.=0.09, t=−12.20, P<0.001 and S.E.=0.08, t=−12.50, P<0.001). In detail, in the immediate perioperative period, RA LA patients reported a pain threshold three-times lower than in patients undergoing the conventional procedure (1.17±0.39 *vs.*

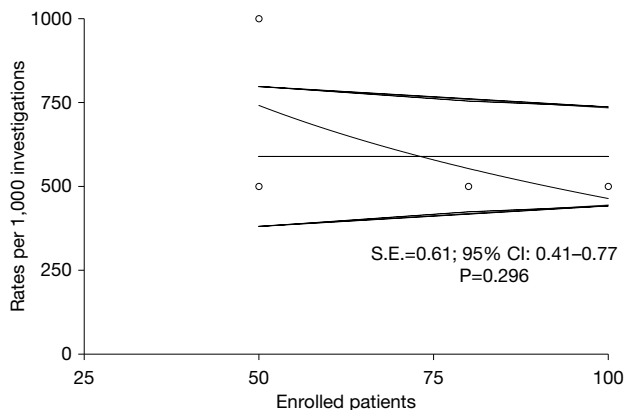Figure 2 Population funnel plot asymmetry test.

4.83±0.70, 95% CI: 3.53–3.79, Df: 3.66, S.E.=0.07, t=54.04, P<0.001) (*Table 2*) (*Figure 5*).

Patients' outcome: secondary endpoints

Hospital stay

Postoperative hospital stay was investigated in two of the articles' panel, enrolling 150 patients (RA-LA *vs.* GA-LA: 75 *vs.* 75). At the weighted-pooled analysis, a strong cumulative effect from one study was discovered (33.33% *vs.* 66.66%; 95% CI: 9.36–52.31, Df: 33.33, P=0.006). For this reason, the analysis failed to demonstrate any superiority or significant difference between techniques,

Figure 3 Cochrane Collaboration's tool for bias risk assessment.

Table 2 Regional *vs.* general anesthesia for laparoscopic appendectomy: outcomes

	RCTs	N pts	RA-LA		GA-LA		RR	95%CI	z-effect	P
			N	% (mean ± SD)	N	% (mean ± SD)				
Arterial hypotension	(10-13)	280	140	5.71	140	0.71	8.00	1.01–63.12	1.97	0.048
Bradicardia	(10-13)	280	140	0.71	140	0	3.00	0.12–73.02	0.67	0.500
Shoulder pain	(10-13)	280	140	2.75	140	6.37	0.35	0.14–0.87	2.27	0.023
PONV	(10-13)	280	140	0.81	140	4.37	0.18	0.41–0.80	2.24	0.024
POUR	(10-13)	280	140	3.57	140	0	11.00	0.61–197.07	1.63	0.103
Postoperative pain	(10-13)	280	140	(1.17±0.39)	140	(4.83±0.70)	NA	3.53–3.79	NA	<0.001
Hospital stay	(11-13)	150	75	(1.00±1.15)	75	(1.00±1.15)	NA	–0.85–0.85	NA	1.000
Time to mobilization (hours)	(12,13)	130	65	(11.75±1.75)	65	(16.60±2.70)	NA	4.06–5.64	NA	<0.001
Bowel sounds resumption (hours)	(12,13)	130	65	(6.95±1.50)	65	(7.85±2.35)	NA	0.21–1.58	NA	0.011

RA-LA, regional anesthesia laparoscopic appendectomy; GA-LA, general anesthesia laparoscopic appendectomy; RCTs, randomised-controlled trials; PONV, postoperative nausea and vomiting; POUR, postoperative urine retention; SD, standard deviation; RR, relative risk; CI, confidence interval; NA, not applicable.

although the comparison did not indicate any substantial disparity between approaches (1.00±1.15 *vs.* 1.00±1.15, 95% CI: –0.85–0.85, Df: 0.00, S.E.: 0.42, P=1.000) (*Table 2*).

Time to mobilization
The time to mobilization was reported in two papers for a total of 130 patients (RA-LA *vs.* GA-LA: 65 *vs.* 65). Also this time, an influent cumulative effect was reported (33.33% *vs.* 66.66%; 95% CI: 9.36–52.31, Df: 33.33, P=0.006), leading to abort further evaluations. However, at the t-paired analysis, RA-LA patients experienced an earlier postoperative mobilization than the control group (RA-LA *vs.* GA-LA: 11.75±1.75 *vs.* 16.60±2.70; 95% CI: 4.06–5.64, Df: 4.85, S.E.: 0.40, P<0.001) (*Table 2*).

Bowel sounds resumption
The resumption of postoperative peristaltic activity was investigated by two RCTs (130 patients). Notwithstanding, a similar cumulative effect than previous analyses was confirmed, locoregional anesthesia allowed a rapid bowel sound restoration in the immediate postoperative period (RA-LA *vs.* GA-LA: 6.95±1.50 *vs.* 7.85±2.35; 95% CI: 0.21–1.58, Df: 0.90, S.E.: 0.35, P=0.011) (*Table 2*).

Discussion

Appendicitis is the most common abdominal emergency

in all age groups (1), as up 10% of the general population experience such condition (15). Open appendectomy has been the gold standard of treatment for many decades, but the efficiency of a laparoscopic approach has gained popularity though still rises debate (16). However, there is strong evidence that the minimal surgical trauma results in less wound infections, less postoperative pain, shorter hospital stay and recovery periods for daily activities (3). Generally, laparoscopic surgery has dramatically reduced postoperative morbidity (17), advocating new challenges for anesthesiologists, such as the management of the effects of pneumoperitoneum, the risk of intraoperative gas embolism and the balancing of an optimal intra- and postoperative analgesia (18). In this setting, regional anesthesia has not gained popularity, rather remaining in an aura of empiricism. Historically, therefore, the use of general anesthesia with controlled ventilation and maintenance of an end-tidal carbon dioxide (EtCO2) around 35mmHg has always been considered the most acceptable technique during laparoscopic procedures. However, despite a general skepticism, locoregional anesthesia has several advantages upon general anesthesia such as a faster recovery, a reduced risk of emesis, an effective postoperative analgesia, a lower incidence of deep vein thrombosis and the absence of endotracheal intubation with subsequent risks of postoperative atelectasis and pneumonia (19). In literature, on the other hand, rare experiences are published about
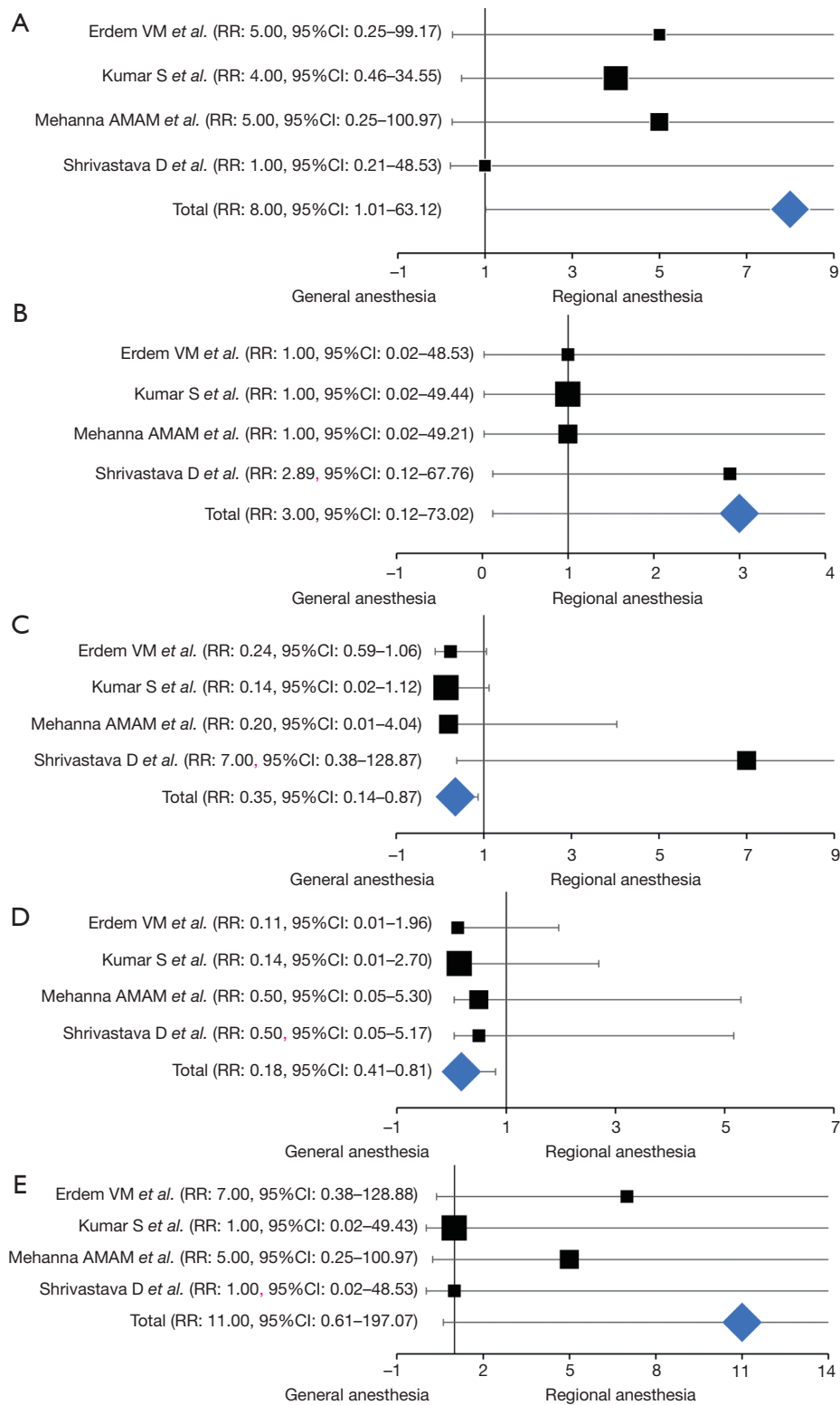
Figure 4 Intraoperative and postoperative patients' outcome: Forrest plot analysis. (A) intraoperative hypotension; (B) intraoperative bradycardia; (C) postoperative shoulder pain; (D) postoperative nausea and vomiting (PONV); (E) postoperative urinary retention (POUR). RR, relative risk, CI, confidence interval.
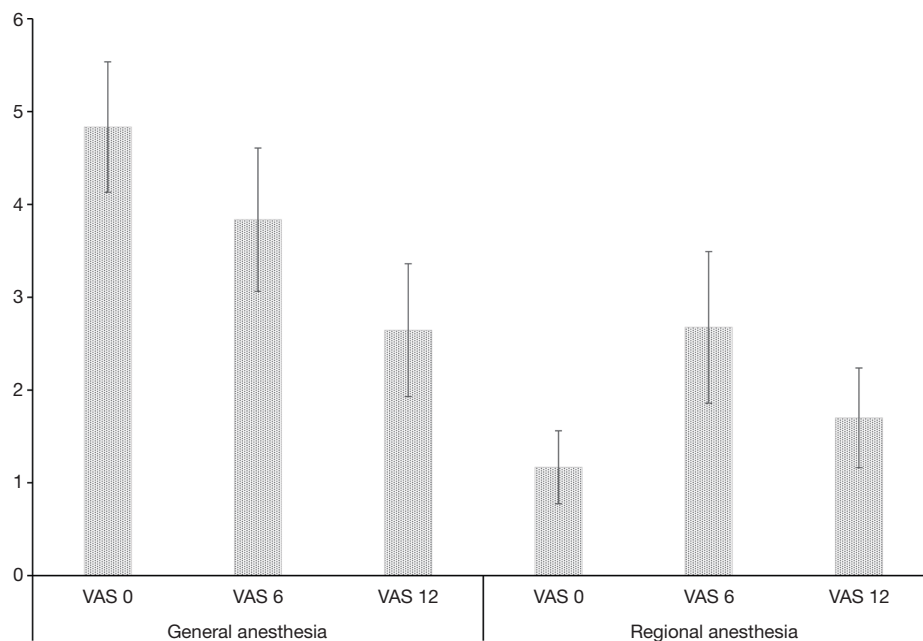
			S.E.	t	p
VAS 0	4.83±0.70	1.17±0.39	0.07	−54.59	<0.001
VAS 6	3.83±0.77	2.67±0.82	0.09	−12.20	<0.001
VAS 12	2.64±0.71	1.71±0.54	0.08	−12.50	<0.001

Figure 5 Postoperative pain: time-interval cohort analysis.

regional anesthesia in laparoscopic surgery and they are usually relegated to small series of monocentric cases or to cohorts of high-risk patients in which the choice of local techniques appears mandatory (7).

The aim of this meta-analysis was therefore to provide some firm points about the safety and efficacy RA during appendectomy. Preliminarily, it is necessary to clarify that Authors decided excluded cohorts of pediatric patients in order to ensure a homogeneous sample enrollment. The eligible RCTs, therefore, included only adult cases with an absent to moderate comorbidity severity scores (ASA I-II) in order to minimize the effect of a potential patients' selection bias.

Cardiovascular impairment is one of the major theoretical issue during RA-LA. In fact, results seem to confirm an increased risk of intraoperative hypotensive events (RR: 8,00, P=0.04) as a consequence of decreased peripheral resistances and venous return secondary to sympathetic blockade. A cumulative incidence of 5.71% was observed in the analysis. On the other hand, regional anesthesia techniques do not influence the onset of

post-operative bradycardias (0.71%, RR: 3.00, P=0.50), consistently with Mehta *et al.* (20) who, in a RCT about the efficacy of spinal anesthesia in laparoscopic cholecystectomies, did not report episodes of bradycardia suggesting cardiovascular variations are partially offset by the effects of pneumoperitoneum through the stimulation of the renin-angiotensin-aldosterone system resulting in an increase in cardiac preload secondary to an increased venous return (21). But, the only independent factor related to the severity of hypotension is the level of sensory block (22), as the maximum risk is directly proportional to the maximum ascension threshold of metameric block (10-13,19,23-26).

Concerning with postoperative shoulder pain, the pathophysiological mechanisms and the induced neuropathic stimulus on the phrenic nerve (C3-C5) of pneumoperitoneum and carbon dioxide by laparoscopy are not completely clear. Although it is common practice to counter ~~the~~ late effects of pneumoperitoneum by instilling warm physiology at the end of the procedure with patient in the Trendelenburg position or by forced pulmonary recruitment maneuvers with open trocars,

van Dijk *et al.* (27), in an RCT including 200 patients undergoing gynecological laparoscopies demonstrated clinical ineffectiveness since there were no differences between the intervention and control group both in the immediate perioperative period (38% *vs.* 50%, P=0.11) and in the first 48 post-operative hours (21% *vs.* 25%, P=0.57). The controversial aspects of laparoscopy-induced shoulder pain raise further issues as no significant topographic abdominal explorations nor technical surgical procedures significantly influence the intensity of postoperative algia. Donatsky *et al.* (28), in a systematic review on laparoscopic cholecystectomies, reported the absence of recommendation to undertake abdominal wall lift techniques in order to reduce wall tension. On the other hand, the Authors recognized the effectiveness of a low-pressure pneumoperitoneum as a precaution to minimize the incidence and severity of pain. However, this strategy cannot be pursued in all patients, such as in obese patients where increased insufflation pressures are required (PP: 12–14 mmHg) in order to overcome parietal inertia and ensure a magnified operating field. Furthermore, a reduced pneumoperitoneum (PP: <10 mmHg) would involve technical problems such as the risk of steric hindrance between ports, the impossibility of performing atraumatic gas-induced dissections and the inability to find anatomical landmarks. According to our analysis, the interventional cohort showed a statistical reduction postoperative shoulder pain (2.75% *vs.* 6.37%. RR: 0.35, P=0.023), suggesting a central role of both prolonged RA-induced analgesia and the lack of a respiratory depression to hypercapnia such as to actively contrast peritoneal hyperinflation.

Postoperative nausea and vomiting (PONV) is one of the significant problems in anesthesia. The pathophysiology of PONV involves several afferent pathways such as chemoreceptor trigger zones, vagal pathways, vestibular systems, midbrain afferents and reflex afferent roots (29). However, there is a wide array of anesthetic, surgical and patients' factors influencing PONV and its still high incidence. Concerning with regional anesthesia, PONV could result from hypotension episodes, anesthetic mixtures, high-level sensory block as far as from the inherent toxicity of local anesthetics (30). According to results, less than 1% of RA LA patients experienced PONV with a significant difference with GA brace (RR: 0.181, P=0.024) which is consistent with a RA-related reported PONV incidence between 0% and 12.50% (31,32). Concerning with early in-hospital course, the only essential side-effect in the RA cohort was urinary retention (RR: 11.00, P=0.10),

confirming regional techniques as risk factors with rates up to 35% in some series (33), as the result of a complex process involving several neural pathways (S2-S3 sacral segments, μ and δ spinal cord receptors), reflexes (detrusor sphincter dissenergy) and central pontine nuclei, where local anesthetics and opioids act (34). But the high relative risk dissonates with a lack of statistical significance. This latter does not seem to be a mere statistical finding as it confirms the depressive action of general anesthetics (muscle relaxants, volatile and sedative-hypnotic anesthetics) on detrusor contraction and micturition reflex.

Further, results of the present analysis revealed VAS score was significantly lower in the postoperative period in RA patients rather than their counterparts (RA-VAS *vs.* GA-VAS: 1.85±0.58 *vs.* 3.77±0.73; P<0.001). Gurudatta *et al.* (35), in a cohort study comparing 50 patients undergoing low abdominal laparoscopic surgery (cystectomy, appendectomy, ovarian drilling) both in GA and RA, reported substantial differences both in the immediate (RA-VAS *vs.* GA-VAS: 0.10±0.30 *vs.* 7.10±0.70; P<0.001) and the early postoperative period (2.10±0.08 *vs.* 5.9±0.70; P=0.009).

Finally, another crucial aspect is postoperative patients' outcome and time-to-resumption from surgery. Although our analysis failed to demonstrate any evidence about hospital stay due to statistical concerns, raw available data allow to deduce that in the modest examined sample, no significant differences between classic and regional anesthesiological conducts were found. These conclusions, therefore, make indirectly to speculate about both the safety and efficacy of RA in laparoscopic appendicectomies (95% CI: –0.85–0.85, Df: 0.00, S.E.: 0.42; P=1.000), since postoperative hospitalization reflect a primary indicator of morbidity as emerged from the subgroup analysis of primary endpoints. Other confirmations come from the evaluation of secondary aims and in particular from the indisputable benefits of an early mobilization (RA-LA *vs.* GA-LA: 11.75±1.75 *vs.* 16.60±2.70, P<0.001) and a prompt resumption of the peristaltic activity (RA-LA *vs.* GA-LA: 6.95±1.50 *vs.* 7.85±2.35, P=0.011).

Study limits

The study design was developed based on a rigorous statistical methodology (PRISMA statements, Cochrane Collaboration Tools). Notwithstanding the absence of a population homogeneity (selection bias) that would have invalidated results (95% CI: 0.41–0.77, P=0.296), current meta-analysis presents some limitations. First, the restricted

cohort of patients could lead to a type 2 statistical error (β >20%) due to the weight percentage of a RCT (12) in the pooled analysis and second, a RCT (11) lacked an exhaustive methodological report, although a rigorous comparison between anesthetic techniques (RA *vs.* GA) was declared.

Conclusions

Locoregional anesthesia laparoscopic appendectomies in adult patients ensure a significant reduction in postoperative adverse events of typical general anesthesiological conduct. The indications for surgical intervention (elective or urgent) do not influence the possibility to perform the procedure safely requiring, instead, a synergy of the operating room team both from a technical and methodological point of view. In conclusions, the analysis clarifies the undoubted role of locoregional anesthesia in laparoscopic visceral surgery, as a valid alternative in the general population and no longer as a strategy reserved for high-risk patients. Further dedicated subpopulation and RCT studies are required for pediatric patients.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/ls.2020.03.02). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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