Continuous thoracic spinal anesthesia with local anesthetic plus midazolam and ketamine is superior to local anesthetic plus fentanyl in major abdominal surgery

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ARTICLE INFO

ABSTRACT

Background: Limited studies have applied thoracic continuous spinal anesthesia in abdominal surgery, relying exclusively on opioids. This retrospective study analyzes 2 different schemes of thoracic continuous spinal anesthesia and postoperative analgesia in elderly patients undergoing major abdominal surgery.

Methods: A total of 98 patients aged ≥75 years were divided into 2 groups. The control group (60 patients) received bupivacaine plus fentanyl, whereas the study group (38 patients) received bupivacaine plus ketamine and midazolam. Both received analogous postoperative continuous intrathecal analgesia. Several perioperative variables were evaluated.

Results: Spinal anesthesia was performed without complications in all patients. Doses of noradrenaline administered, incidence of respiratory depression, need for intraoperative sedation, and time to first flatus were significantly reduced in the bupivacaine plus ketamine and midazolam group.

Conclusion: In a population of frail, elderly patients, thoracic continuous spinal anesthesia with local anesthetic plus midazolam and ketamine was superior to local anesthetic plus fentanyl. In the group receiving local anesthetic plus midazolam and ketamine, the incidence of respiratory depression was reduced, and doses of norepinephrine and intraoperative sedating medications were lower. Intraoperative anesthesia and postoperative analgesia were similar in both groups.

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INTRODUCTION

Over the past century, the constant increase in life expectancy has been responsible for a corresponding rise in disease management and operative procedures in older adults [1]. Although general anesthesia (GA) is routinely used for major abdominal surgery, it is accompanied by significant morbidity and mortality, especially in elderly patients suffering from multiple severe systemic diseases (American Society of Anesthesiologists [ASA] classification III or above) [2]. Accordingly,

regional anesthesia, particularly neuraxial blockade, has gained popularity as an effective and safe technique that might provide improved outcomes in terms of perioperative morbidity and mortality compared to GA, although conclusive, long-term evidences are still missing [3–5]. Spinal anesthesia and epidural anesthesia are the 2 main types of neuraxial blockade and have been shown to decrease respiratory and cardiac complications [3,6] and the neuroendocrine stress response [7], to improve effective pain control [8], to promote return of gastrointestinal function [8,9], to protect against thromboembolic events [10], and to facilitate early patient mobilization. In particular, continuous spinal anesthesia (CSA), by placing a microcatheter in the subarachnoid space, ensures a better control of anesthesia level with increased sensory-motor blockade, improved cardiovascular and respiratory stability, and a reduced requirement for local anesthetics along with a lower risk of toxicity, representing noteworthy advantages of this method compared to continuous epidural, combined spinal-epidural,

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and GA [11]. The possibility of maintaining continuous postoperative spinal analgesia provides optimal pain management, sparing intravenous nonsteroidal anti-inflammatory drugs and opioids. Differently from lumbar spinal anesthesia, the safe use of thoracic spinal anesthesia in high-risk older patients undergoing surgery of the upper abdomen is described in only a few case reports and case series [12–14]. However, CSA has been implicated in specific complications, such as infection, postdural puncture headache, spinal hematoma, and cauda equina syndrome [15]. It was not demonstrated unequivocally that the spinal microcatheter itself was the cause of all these complications; hence, the technique has been used in clinical practice with renewed interest.

For all these reasons, in our geriatric medical center, thoracic continuous spinal anesthesia (TCSA) has emerged as the leading technique to perform several abdominal surgical procedures in elderly patients at substantially elevated perioperative risk where the demonstrated benefits greatly overwhelm the potential risks associated with the procedure itself [8].

Because a recent series from our Institution conducted on a large cohort of elderly patients undergoing several types of abdominal and urologic surgical procedures already demonstrated the feasibility and efficacy of TCSA [14], this study aims at comparing 2 different regimens of spinal anesthesia and postoperative continuous analgesia through the analysis of several perioperative and postoperative outcomes in elective and urgent abdominal surgery.

MATERIALS AND METHODS

Study Design and Population. A retrospective cohort study was conducted on all patients aged ≥75 years undergoing urgent and elective abdominal surgery under the technique of TCSA at the Italian National Research Center on Aging, the only institute specifically focused on geriatric care and gerontological research in Italy, between 2017 and 2019. For this reason, the cases reviewed in our study presenting with multiple comorbidities, particularly ischemic cardiac diseases, congestive heart failure, severe chronic obstructive pulmonary diseases (COPD), complicated diabetes mellitus, and chronic kidney diseases carrying a high risk for GA [1], were referred to our center and discussed by the relevant multidisciplinary team, and after extensive consideration of life/risk benefits, a collective decision was made to perform surgery under this technique. The study was approved by the local Ethics authority, and written informed consent was obtained from all subjects or a legal surrogate. We defined *urgent surgery* as an operative procedure that was meant to prevent morbidity or mortality, was not booked from an outpatient clinic (elective basis), and required an unplanned operation upon the patient's admission to the hospital.

Patients in the control group received a neuraxial combination of a local anesthetic, represented by levo-bupivacaine and/or hyperbaric bupivacaine, and fentanyl (LA + F). In the study group, the opioid was replaced by 2 different adjuvants: midazolam and ketamine (LA + M + K). The first scheme was used from January 2017 to October 2018; thereafter, the second regimen was adopted.

All the variables analyzed are listed in Table 1.

Anesthesiologic Technique and Postoperative Analgesic Regimen. Preloading was achieved by administering 500 mL of crystalloids. After sterile thoracic-lumbar field preparation with the patient sitting up or in a lateral decubitus, the correct intervertebral space, located between T6 and T12 depending on the type of surgical procedure, was identified using fully aseptic techniques. A Spinolong kit (Temena, Italy) was used for CSA. The kit included a 21G Tuohy-shaped spinal needle and 24G intrathecal catheter. After free flow of cerebrospinal fluid was obtained, the catheter was inserted 3–4 cm beyond the tip of the needle. Procedure-related paresthesias, pain, or any difficulty during spinal puncture and catheterization was recorded in each case. Once inserted, the catheter was secured and covered with a sterile transparent dressing from the insertion site to the ipsilateral shoulder,

Table 1
Variables analyzed

Preoperative	Operative	Postoperative
Demographics	Rate of conversion from TCSA to GA	Use of NE and maximum dose
BMI		
ASA class [16]	Surgical diagnosis	Need for mechanical ventilation
Comorbidities	Operative procedure	
Charlson Comorbidity Index [17]	Total operating time	Pain
	Frequency of relaparotomy	Respiratory depression
	Type, number, and total dose of neuraxial local anesthetics used	Headache
		Anastomotic dehiscence
	Necessity of intravenous sedation	Main complications organ related
	Mean HR	
	Mean SpO₂	Overall morbidity
	Diuresis	In-hospital mortality
	Fluid infusion	Use and dosage of intravenous nonopioid analgesics
	Use of NE and maximum dose	
	Occurrence of pain	
	No. of patients transfused	Time to first flatus and to solid oral intake [18]
	No. of PBRCs units transfused	Length of hospital stay
		No. of patients transfused
		No. of PRBCs units transfused

BMI, body mass index; HR, heart rate; NE, norepinephrine; SpO₂, pulse oximeter oxygen saturation.

and the catheter was connected to a bacterial microfilter. An arterial line was inserted in all patients prior to the commencement of anesthesia for direct blood pressure monitoring and blood sampling. A central venous line catheter was inserted if clinically indicated.

Hyperbaric bupivacaine 0.5% and/or levo-bupivacaine 0.5% not diluted at a dose of 2.5 mg were injected intrathecally followed by an equal dose 3 minutes later. The administration of neuraxial local anesthetics was preceded by different adjuvants according to the group. In the LA + F group, fentanyl (0.3 μg/kg) was given intrathecally, whereas in the LA + M + K group, the neuraxial anesthetic was associated with ketamine (0.25 mg/kg) and midazolam (0.03 mg/kg). The level of the sensory blockade was tested using pinprick tests, and if needed, further incremental doses of 0.4–0.5 mL of the same concentration of local anesthetic were given until a sensory T4 level was achieved, allowing surgery to begin.

During surgery, an analogous incremental bolus dose of local anesthetic was given 60 minutes after the first administration and when the patient complained of pain or when sensory block regressed at least 2 segments. In the case of patient anxiety and discomfort, sedation was achieved with an intravenous midazolam bolus (0.02–0.05 mg/kg) or a continuous infusion of propofol (1–3 mg/kg/h).

All patients were spontaneously breathing in Venturi masks on 28%–40% inspired oxygen fraction and monitored continuously by clinical observations, including sensory block and invasive hemodynamic monitoring, in addition to standard monitoring consisting of electrocardiogram, heart rate, respiratory rate, pulse oximetry, body temperature, arterial blood gases and acid-base balance, urinary output, and blood loss. All data were recorded at 5-minute intervals during surgery. *Hypotension*, defined as a decrease in systolic blood pressure of more than 15% of the basal preanesthetic value, was managed with a continuous infusion of noradrenaline titrated to maintain a mean arterial pressure (MAP) greater than 65 mm Hg.

Postoperative continuous analgesia started 30 minutes before the end of surgery through continuous drug administration by an elastomeric pump connected to the catheter.

Two main regimens were used, similar to those used in spinal anesthesia. In the control group (LA + F), levo-bupivacaine 60 mg (0.166%) was associated with fentanyl 75 μg (concentration 2 μg/mL) in 0.9% saline at a total of 36 mL, whereas in the study group (LA + M + K), levo-bupivacaine 60 mg (0.166%) was associated only with midazolam 4 mg in 0.9% saline at a total of 36 mL. The infusion rate was 0.2–0.8 mL/h, and the duration was 72 hours.

Because our Institution at the time of writing was not equipped with an intensive care unit, at the end of surgery, the patients were transferred to the postanesthesia care unit, where they all remained for at least 6 hours, and then to the surgical unit, including those requiring vasopressor support. Indeed, our surgical team has been totally trained in managing postoperative continuous infusion of vasopressor amines when used to contrast the hypotensive effects of continuous postoperative analgesia in patients otherwise awake and not intubated, as it was the case in our series. The monitoring used during surgery was also applied during the immediate postoperative period in the postanesthesia care unit.

Measurements. The preanesthetic risk was scored according to the ASA physical status classification system [16]. The Charlson Comorbidity Index was used to determine the burden of comorbidities [17]. Preoperatively, patients were taught how to evaluate their own pain intensity using the visual analogue scale (VAS), scored from 0 to 10 (where 0 = no pain and 10 = the worst pain imaginable). Pain was assessed intraoperatively and postoperatively every 2 hours for the first 12 hours and then every 6 hours until postoperative day 3. Any request for intravenous painkillers was noted. Only VAS pain scores greater than 4 were considered notable, and intravenous analgesics (paracetamol 1 g or nonsteroidal anti-inflammatory drugs) were administered.

Resolution of postoperative ileus was measured by the time required to observe first flatus together with the ability to tolerate oral intake [18].

The level of sedation was assessed at the same time points on a 5-point scale: 0 = alert, 1 = easily arousable, 2 = awakens after tactile stimulation, 3 = awakens after verbal stimulation, and 4 = not arousable. Complications were classified according to Clavien and Dindo criteria [19], and overall morbidity was assessed with the Comprehensive Complication Index [20].

Respiratory depression was defined as a respiratory rate < 10 breaths per minute, oxygen saturation < 90% by pulse oximetry lasting at least 3 minutes, hypercapnia ($pCO_2 > 50$ mm Hg), or a change from baseline end-tidal $CO_2 > 10$ mm Hg. Monitoring was performed for a minimum of 24 hours after administration of neuraxial drugs, at least once per hour for the first 12 hours and then every 2 hours for the next 12 hours. After 24 hours or after discontinuation of the postoperative analgesia, the frequency of monitoring was dictated by the patient's overall clinical condition and concurrent medications, as suggested by the ASA guidelines [21].

Acute respiratory failure was defined as a clinical condition characterized by difficulty breathing associated with the following ABG parameters: $PO_2 < 60$ mm Hg while breathing room air or $pCO_2 > 50$ mm Hg, with pH <7.35. In the presence of severe COPD and chronic respiratory failure whose baseline pO_2 is less than 60 mm Hg, a pO_2 that is 10 mm Hg below baseline and any degree of acidosis (pH <7.35) were considered proof of acute respiratory failure [22]. Acute heart failure and acute kidney failure were defined according to 2016 European Society of Cardiology guidelines [23] and 2012 Kidney Disease: Improving Global Outcomes clinical practice guidelines [24], respectively.

All patients were visited daily to assess any nerve root injury (radiculopathy, back pain, cauda equina), central nervous system complications (meningitis, spinal abscess, spinal hematoma), and postdural puncture headache.

Statistical Analysis. Normally distributed continuous data were reported as the mean ± standard deviation (SD) and compared using the 2-sided Student t test. Non-normally distributed continuous data were reported as the median and range and compared using the Mann-Whitney test. Categorical variables were analyzed with the χ^2 test with the Yates correction or Fisher exact test, depending on best applicability. IBM SPSS Statistics version 24 (SPSS Inc, Chicago, IL) was used for statistical analysis.

RESULTS

Ninety-eight patients were included in the study, of which 60 patients were enrolled in the LA + F group and 38 in the LA + M + K group. All anesthetic and surgical procedures were completed without any intraoperative major complications, and there were no cases in which it was necessary to convert from CSA to GA.

After analysis of both groups, no significant difference was found in pre- and intraoperative parameters except for the type of local anesthetics used ($P < .001$) and for the cumulative dose of local anesthetic administered, which was significantly higher in the LA + M + K group ($P = .034$) (Tables 2 and 3).

Regarding the intraoperative hemodynamic parameters, MAP, mean SpO_2, diuresis, and fluid infusion did not differ between the 2 groups, whereas only the mean heart rate was significantly reduced in the LA + M + K group ($P = .013$), as listed in Table 3. In relation to vasopressor requirements, the number of patients who required an intraoperative vasopressor support was similar in both groups, whereas the number requiring vasopressor amines in the postoperative period ($P = .017$) and the maximum dose of noradrenaline administered during ($P = .048$) and after surgery ($P = .007$) were significantly reduced in the study group (Tables 3 and 4).

Regarding perioperative analgesia, VAS scores recorded intraoperatively were less than 4 in all patients, and no significant difference was found in the incidence of pain or the administration of intravenous analgesics after surgery as confirmed by the mean VAS registered and by the doses of analgesics used in both groups (Tables 3 and 4). Otherwise, the frequency of respiratory depression was significantly elevated in the LA + F group ($P = .037$), whereas the intraoperative administration of intravenous sedation drugs ($P < .001$) and the time to first flatus ($P < .001$) were significantly reduced in the LA + M + K group, as shown in Tables 3 and 4.

Although there was no significant difference between the 2 groups in the number of patients who required at least 1 U of packed red blood cells (PRBCs) both during and after surgery, those in the study group required more units per capita ($P = .042$), as shown in Tables 3 and 4. The incidence of anastomotic dehiscence, general and organ-related complications, and all-cause in-hospital mortality; the time to solid oral intake; and the length of hospital stay did not differ between the groups (Table 4).

Table 2
Preoperative variables analyzed

	LA + M + K group (n = 38)	LA + F group (n = 60)	P value
Age (y), mean ± SD	84.4 ± 6.7	85.5 ± 6.1	.411
Male, *n* (%)	19 (50)	30 (50)	1
BMI (kg/m^2), median (range)	24 (17.6–45)	22.8 (17–39)	.547
Comorbidity, *n* (%)			
Cardiac disease	27 (71.1)	38 (63.3)	.570
Ischemic cardiac disease	17 (62.9)	22 (57.8)	.560
CHF class II or III	12 (44.4)	18 (47.3)	.952
COPD requiring LTOT	17 (44.7)	29 (48.3)	.888
CNS disease	10 (26.3)	26 (43.3)	.137
Stroke	6 (60)	16 (61.5)	.313
Neurocognitive disorder	3 (30)	9 (34.6)	.466
Parkinson disease	2 (20)	5 (19.2)	.863
Complicated type 2 diabetes	11 (28.9)	18 (30)	1
Chronic renal failure	12 (31.6)	11 (18.3)	.815
Charlson Comorbidity Index, mean ± SD	7.5 ± 2.6	8 ± 2.6	.414
ASA score, *n* (%)			
2	2 (5.3)	3 (5)	
3	29 (76.3)	40 (66.7)	.537
4	7 (18.4)	17 (28.3)	

CHF, congestive heart failure; *CNS*, central nervous system; *LTOT*, long-term oxygen therapy.

Table 3
Operative variables analyzed

	LA + M + K group (n = 38)	LA + F group (n = 60)	P value
Surgical diagnosis, n (%)			
Colorectal cancer	16 (42.1)	33 (55)	
Gastric cancer	9 (23.7)	7 (11.7)	
Non-neoplastic bowel obstruction	4 (10.5)	8 (13.3)	.265
Gallbladder disease	5 (13.2)	3 (5)	
Other*	4 (10.5)	9 (15)	
Urgency, n (%)	13 (34.2)	33 (55)	.072
Surgical procedure, n (%)			
Colectomy	18 (47.4)	39 (65)	
Gastrectomy	9 (23.7)	5 (8.3)	
Adhesiolysis†	4 (10.5)	4 (6.7)	.053
Cholecystectomy	5 (13.2)	3 (5)	
Other‡	2 (5.3)	9 (15)	
Operative time (min), mean ± SD	126 ± 38	123 ± 45	.672
Relaparotomy, n (%)	4 (10.5)	8 (13.3)	.761
Conversion to GA, n (%)	0 (0)	0 (0)	n.a.
Local anesthetics			
Type, n (%) levo-bupivacaine	7 (18.4)	37 (61.7)	<.001
Hyperbaric bupivacaine	35 (92.1)	25 (41.7)	<.001
Number (>1), n (%)	4 (10.5)	2 (3.3)	.203
Cumulative dose, median (range)	9.5 (4–25)	7.5 (5–15)	.034
Hemodynamic			
MAP, mean ± SD	75.4 ± 7.1	72.8 ± 8.5	.120
HR, median (range)	70 (55–92.5)	75 (57.5–115)	.013
SpO$_2$, median (range)	98 (92–100)	97 (91.5–100)	.543
Diuresis (mL/kg/h), mean ± SD	0.96 ± 0.3	0.9 ± 0.3	.373
Fluid infusion (mL/kg/h), median (range)	15.6 (6.6–33)	18.6 (9–63.6)	.059
Vasopressor support			
NE use, n (%)	27 (71.1)	50 (83.3)	.243
Max dose,§ median (range)	0.09 (0.02–0.3)	0.13 (0.04–0.59)	.048
Pain with VAS > 4, n (%)	0	0	n.a.
Intravenous sedation, n (%)	17 (44.7)	57 (95)	<.001
PRBCs, n (%)	6 (15.8)	14 (23.3)	.519

* Complicated acute diverticulitis and ischemic colitis, ovarian neoplasm with abdominal compartmental syndrome, postincisional hernia, colostomy, perforated duodenal diverticulum, and enterocutaneous fistula.
† With or without intestinal resection.
‡ Hysterectomy with ovariosalpingectomy, laparoscopic repair of postincisional hernia, stoma reversal, internal bypass, and suture of duodenum.
§ Expressed in μg/kg/min.

No patient needed mechanical ventilation in the postoperative setting or complained of headache and any other neurologic sequelae related to spinal anesthesia (Table 4).

DISCUSSION

This is the first study to report the use of "opioid-free" TCSA for elective and urgent abdominal surgery in older patients with comorbidities. Our study confirms that CSA can be used as a primary anesthesiologic method for major abdominal surgery in elderly patients at serious risk for mortality and morbidity with GA [12–14].

Our data show that this regimen may have significant perioperative advantages compared to the conventional scheme that implies the administration of an intrathecal opioid, mainly in the field of vasopressor amine need, respiratory depression, and bowel recovery time, without impairing other areas such as pain management, overall morbidity, and mortality.

Indeed, many studies described the use of CSA in high-risk patients undergoing cardiac, vascular, orthopedic, pelvic, and abdominal surgery who would be considered unlikely to survive general anesthesia [11,12]. This method provides significantly improved hemodynamic control, avoids invasive airway management, enhances intraoperative analgesia, and allows the maintenance of a postoperative analgesia with superior efficiency and minimal effect on mental status, carrying a

Table 4
Postoperative variables analyzed

	LA + M + K group (n = 38)	LA + F group (n = 60)	P value
Vasopressor support			
NE use, n (%)	18 (47.4)	44 (73.3)	.017
Max dose,* median (range)	0.08 (0.01–0.24)	0.12 (0.01–0.7)	.007
Analgesia			
Pain with VAS > 4, n (%)	15 (39.5)	23 (38.3)	1
VAS, mean ± SD	6.24 ± 1.21	6.3 ± 1.09	.840
Intravenous analgesics, n (%)	15 (39.5)	23 (38.3)	1
Analgesic doses, n (%)			
1	8 (53.3)	9 (39.1)	.598
>1	7 (46.7)	14 (60.9)	
Need for mechanical ventilation, n (%)	0 (0)	0 (0)	n.a.
Respiratory depression, n (%)	2 (5.2)	14 (23.3)	.037
Time to first flatus (p.o. day), median (range)	2 (1–7)	3 (1–7)	<.001
Solid oral intake (p.o. day), median (range)	5 (1–37)	5 (1–12)	.686
P.o. complications, n (%)	32 (84.2)	56 (93.3)	.179
Clavien-Dindo grade, n (%)			
I	2 (6.2)	0	
II	20 (62.5)	37 (66.1)	
III	2 (6.2)	4 (7.1)	.218
IV	4 (12.5)	3 (5.4)	
V	4 (12.5)	12 (21.4)	
CCI, median (range)	30.2 (8.7–100)	29.6 (20.9–100)	.359
Anastomotic dehiscence,† n (%)	5 (17.9)	6 (14)	.742
Anemization,‡ n (%)	12 (31.6)	23 (38.3)	.643
Infections, n (%)	10 (26.3)	13 (21.7)	.776
Acute respiratory failure, n (%)	5 (13.2)	14 (23.3)	.327
Acute cardiac failure, n (%)	4 (10.5)	13 (21.7)	.252
Arrhythmias (AFib/AF), n (%)	4 (10.5)	10 (16.7)	.582
Acute kidney failure, n (%)	2 (5.3)	8 (13.3)	.308
Headache, n (%)	0 (0)	0 (0)	n.a.
Other complications,§ n (%)	8 (21.1)	4 (6.7)	.055
PRBC, n (%)	12 (31.6)	23 (38.3)	.643
PRBC units,¶ median (range)	2.5 (1–9)	2 (1–8)	.042
Hospital stay (d), median (range)	10 (3–49)	12 (1–53)	.375

AF, atrial flutter; AFib, atrial fibrillation; CCI, comprehensive complication index; p.o., postoperative.
* Expressed in μg/kg/min.
† Calculated in patients with gastrointestinal anastomosis.
‡ Requiring blood transfusions.
§ Acute urinary retention, PONV, acute hypertension, and transient ischemic attack.
¶ Calculated in patients transfused.

considerable reduction in major postoperative complications compared to GA [3–5], particularly in the elderly. TCSA reinforces all these benefits in abdominal surgery due to its selective spinal block allowing a rapid onset of action and a reduced dose of local anesthetic required [25]. Its safety was demonstrated by magnetic resonance imaging investigations on the anatomy of the thoracic spinal cord that lies more anteriorly from mid to lower thoracic level [26], thus facilitating the insertion of a needle and the advancement of a flexible catheter in the subarachnoid space with relatively low risk of neurological damage [25,27]. In particular, in a population of 300 patients undergoing spinal thoracic anesthesia for elective surgery, lower incidence of paresthesia was reported during spinal puncture conducted with a cut needle without an introducer similar to that used in our series compared to a pencil point needle with an introducer (6.6% vs 12%) [27]. No neurologic injuries or sequelae occurred during this study. In addition, the authors document a similar incidence of paresthesia to that reported in lumbar spinal anesthesia [27].

Nevertheless, there are only a few reports in the literature regarding the use of TCSA in abdominal surgery, mainly requiring a higher level of sensorial block [12–14]. All these series describe a regimen of spinal anesthesia based on a combination of intrathecal local anesthetics and opioids, both intraoperatively and postoperatively. Unfortunately, the use

of intrathecal opioids is associated with adverse effects such as respiratory depression, urinary retention, pruritus, nausea, vomiting, and delirium [28]. Therefore, it can be helpful to develop a technique that allows sparing of the neuraxial opioid, replacing it with other adjuvants. This strategy was based on limited but encouraging evidences that midazolam and ketamine significantly improve the duration and quality of spinal anesthesia, reduce the onset time of sensory and motor block, provide a mild intraoperative sedative effect, ensure prolonged perioperative analgesia due to delayed recovery time of sensory block, and decrease the incidence of postoperative nausea and vomiting (PONV) without negative effects on perioperative hemodynamics, significant adverse effects, and neurotoxicity [29–31].

To the best of our knowledge, this is the first study on CSA that compares 2 different schemes applied both in neuraxial anesthesia and in postoperative analgesia, one based on the combination of an intrathecal local anesthetic and fentanyl and the other on the association of a local anesthetic plus midazolam and ketamine. In our research, we investigated several outcomes aiming to determine the superiority of the second regimen. Our results indicate that, with both methods, acceptable intraoperative hemodynamics were generally ensured by the administration of moderate doses of vasopressor amines, as demonstrated by the recorded parameters. Nevertheless, the "opioid-free" strategy provided significant benefits in terms of perioperative vasopressor support with inferior doses of noradrenaline administered intra- and postoperatively and fewer patients requiring postoperative vasopressor support. This point might be of notable value because the reduction in renal and splanchnic perfusion induced by all catecholamines and their toxic effects, in particular myocardial ischemia and arrhythmias, increase the risk of organ failure and consequently of postoperative mortality [32]. Despite this affirmation, in our series, postoperative complications potentially of ischemic nature, such as acute kidney injury and anastomotic dehiscence and cardiac morbidity, did not differ between the 2 groups even if it is not possible to provide a definitive conclusion because of the low incidence reported in our study.

In addition, comparable perioperative analgesia was observed in both groups as stated by all parameters used to evaluate this outcome during and after surgery: incidence of pain, VAS, administration of intravenous nonopioid analgesics, and their doses. A regimen of "opioid-free" postoperative continuous analgesia, such as that adopted in our study, which might provide similar results in pain management allowing at the same time to avoid the serious adverse effects of intrathecal opioids, can be a precious resource in older surgical patients. The potent analgesic effect of intrathecal midazolam may be induced by the release of an endogenous opioid acting at spinal δ receptors combined with its predominant agonistic action on the GABA-A receptors located in lamina II of dorsal horns of human spinal cord [29]. Minimal systemic absorption and the absence of systemic and neurological adverse effects are the other remarkable advantages of this benzodiazepine when used intrathecally compared to opioids [29].

In connection with what has already been stated, the incidence of perioperative respiratory depression was significantly increased in the LA + F group. Even if these data might be confounded by hypoventilation and hypoxemia from intraoperative intravenous sedation and surgery itself, this represents certainly the most serious complication of opioids, regardless of the route of administration [21,28]. Therefore, in our opinion, all strategies to minimize their use should be encouraged.

Likewise, the need for intraoperative sedation reached statistical significance, meaning that intravenous sedation drugs were administered to a significantly reduced number of patients in the LA + M + K group during surgery. This relationship between the type of spinal anesthesia and sedation is easy to explain because intrathecal midazolam and ketamine possess an intrinsic anxiolytic effect according to the literature [29–31]. This is another potential noteworthy benefit of this regimen because the elderly represents the group with the highest risk of serious adverse effects from systemic benzodiazepines, and the 2019

American Geriatrics Society's updated Beers Criteria continue to list benzodiazepines and barbiturates as drugs to avoid in in patients more than 65 years of age with a strength of recommendation classified as strong in all ambulatory, acute, and institutionalized settings of care [33].

Similarly, we observed increased consumption of units of PRBCs per capita in this class of patients. This may be related to the increased proportion of patients affected by ischemic heart disease in whom hemoglobin thresholds for PRBC transfusion are generally reduced [34].

Regarding the recovery of gastrointestinal function, a recent, extensive Cochrane review highlights how an epidural scheme containing solely a local anesthetic accelerates the return of gut function compared with a scheme containing opioids [35]. To be effective, the epidural regimen needs to be administered after surgery—not solely intraoperatively. Therefore, we hypothesized that a similar mechanism may apply in our series even if we were not able to find trials comparing this outcome in the field of CSA. In addition, the literature recognizes the beneficial effect that postoperative epidural analgesia might have on the resolution of postoperative ileus and on the incidence of PONV in comparison with a systemic, opioid-based postoperative analgesia [36]. Whatever the reason, this is another point of fundamental importance in older patients undergoing abdominal surgery because prolonged postoperative ileus may lead to delayed recovery and protracted hospital stay. Nevertheless, no difference was observed in the time to postoperative feeding. This may be related to a discrete percentage of gastric surgical procedures in our series where our protocols establish to perform routine contrast radiography on the fifth postoperative day before resuming oral nutrition.

After analyzing the other complications, we noted an increasing trend of acute hypertension in the study group and of PONV in the control group, although it was not statistically significant. Acute hypertension might be related to the stimulant effect of ketamine on the orthosympathetic system even if low doses of intrathecal ketamine such those used in our series should not present systemic or neurologic toxicity according to literature [30]. Indeed, adverse effects of intrathecal ketamine were reported in animal studies when doses of at least 0.7 mg/kg were applied and repeated for several days, and it was not clear if the neurotoxicity observed was related to preservatives contained in the solutions used or directly to the amount of ketamine used. Even if the dose applied in our study of 0.25 mg/kg is greater than that used in the cited study of 0.1 mg/kg [30], it is considerably inferior to that responsible for important adverse effects. Similarly, PONV might be directly related to the administration of intrathecal opioids [28]. However, the low frequency observed cannot absolutely provide definitive conclusions. In addition, all these patients underwent major abdominal surgery represented by gastric or colorectal resection, and many other factors might have contributed in developing the complications mentioned above.

Moreover, we were not able to identify any significant difference in the incidence of major postoperative complications, all-cause in-hospital mortality, and length of hospital stay between the 2 groups. The above-cited Cochrane review reports a similar incidence of gastrointestinal anastomotic leak with the 2 different schemes of epidural anesthesia described [35]. However, to the best of our knowledge, no studies have analyzed these clinical end points in patients undergoing spinal anesthesia. The high rates of morbidity and mortality observed in our series are related to the remarkable baseline vulnerability of the population studied, exposed to the serious insults accompanying abdominal surgery.

In our series of TCSA procedures, we reinforced the findings that the 2 local anesthetics, levo-bupivacaine and bupivacaine, are clinically comparable in terms of efficacy, potency, and hemodynamic response, as several studies have indicated during lumbar spinal anesthesia [37,38], lacking definitive assumptions on the superiority of one over the other. Nevertheless, we identified a discrepancy in the cumulative dose of neuraxial local anesthetic used in the 2 groups, with a greater

amount of drug consumed in the LA + M + K group. Although our data confirm that the addition of an intrathecal opioid can reduce the median effective dose of the local anesthetic [39], it appears that this does not apply to the other adjuvants used in the LA + M + K group, in contrast to what has been reported in the literature [40].

Finally, in our sample, we did not report any severe direct complications of the technique (eg, epidural hematomas, infection, or cauda equina syndrome) [15], adding more data on its safety when used by experienced physicians.

There are several limitations to this study. Although the data were prospectively collected, the analysis was retrospective in nature and lacks of a control group undergoing GA to compare our findings. In addition, the low frequency of some variables analyzed, such as anastomotic dehiscence, acute hypertension, and PONV, might be responsible for a type II error. Although we evaluated the largest sample of comorbid older patients so far, we encourage further studies to confirm our results.

In conclusion, in accordance with previous findings, our experience suggests that CSA can be performed effectively and safely in high-risk elderly patients undergoing major abdominal surgery, representing a suitable option to GA in this particular subgroup of patients.

This study identifies several remarkable advantages of a spinal anesthesia and postoperative analgesia scheme that replaces intrathecal opioids with midazolam and ketamine. In particular, a minor perioperative use of vasopressor agents and incidence of respiratory depression emerged as being the most important clinically, together with equivalent perioperative pain control and faster recovery of bowel function. We strongly believe that these benefits are the result of the different adjuvants used, midazolam and ketamine, and we anticipate that our findings will encourage other clinicians to extend the use of "opioid-free" TCSA in selected high-risk patients undergoing major abdominal surgery. Because, at the time of writing, there is no specific consensus on the different techniques of CSA described, larger prospective controlled studies are required to determine the best clinical and surgical criteria for TCSA to optimize the use and type of neuraxial local anesthetics and adjuvants, with the goal of minimizing perioperative complications, particularly in comorbid older patients.

Author Contribution

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Conflict of Interest

None to declare.

Funding Sources

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