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The primary aim of the *World Journal of Clinical Cases (WJCC)* is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

The *WJCC* mainly publishes case reports, case series, research results and findings in the field of clinical medicine covering a wide range of topics including diagnostic, therapeutic, and preventive modalities.

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Prospective Study

Analysis of the postoperative hemostatic profile of colorectal cancer patients subjected to liver metastasis resection surgery

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Patients were not required to give informed consent to the study because the analysis used anonymous data that were obtained after each patient agreed to treatment by written consent.

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Abstract**BACKGROUND**

Liver resection surgery has advanced greatly in recent years, and the adoption of fast-track programs has yielded good results. Combination anesthesia (general anesthesia associated to epidural analgesia) is an anesthetic-analgesic strategy commonly used for the perioperative management of patients undergoing surgery of this kind, though there is controversy regarding the coagulation alterations it may cause and which can favor the development of spinal hematomas.

AIM

To study the postoperative course of liver resection surgery, an analysis was made of the outcomes of liver resection surgery due to colorectal cancer metastases in our centre in terms of morbidity/mortality and hospital stay according to the anesthetic technique used (general *vs* combination anesthesia).

METHODS

A prospective study was made of 61 colorectal cancer patients undergoing surgery due to liver metastases under general and combination anesthesia between January 2014 and October 2015. The patient characteristics, intraoperative variables, postoperative complications, evolution of hemostatic parameters, and stay in intensive care and in hospital were analyzed.

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RESULTS

A total of 61 patients were included in two homogeneous groups: general anesthesia ($n = 30$) and combination anesthesia (general anesthesia associated to epidural analgesia) ($n = 31$). All patients had normal coagulation values before surgery. The international normalized ratio (INR) in both the general and combination anesthesia groups reached maximum values at 2448 h (mean 1.37 and 1.45 *vs* 1.39 and 1.41, respectively), followed by a gradual decrease. There was less intraoperative bleeding in the combination anesthesia group (769 mL) than in the general anesthesia group (1200 mL) ($P < 0.05$). Of the 61 patients, 38.8% in the general anesthesia group experienced some respiratory complication *vs* 6.6% in the combination anesthesia group ($P < 0.001$). The time to gastrointestinal tolerance was significantly correlated to the type of anesthesia, though not so the stay in critical care or the time to hospital discharge.

CONCLUSION

Epidural analgesia in liver resection surgery was seen to be safe, with good results in terms of pain control and respiratory complications, and with no associated increase in complications secondary to altered hemostasis.

Key words: Hepatectomy; Epidural analgesia; Perioperative complications; Epidural hematoma; Multimodal rehabilitation; Outcomes

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Core tip: This is a study of morbidity/mortality and hospital stay according to the anesthetic technique used (general *vs* combination anesthesia) in liver resection surgery in patients with colorectal cancer metastases. Epidural analgesia in liver resection surgery was seen to be safe, with good results in terms of pain control and respiratory complications, and with no associated increase in complications secondary to altered hemostasis. The time to gastrointestinal tolerance was significantly correlated to the type of anesthesia, though not so the stay in critical care or the time to hospital discharge.

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INTRODUCTION

There is currently enough experience to consider liver resection as the treatment of choice for some colorectal cancer patients with liver metastases. Combination anesthesia (general anesthesia associated to epidural analgesia) is an anesthetic/analgesic strategy commonly used for the perioperative management of liver surgery patients. Its inclusion in fast-track liver surgery protocols has yielded good results in terms of morbidity and hospital stay^[1-3]. However, there is some controversy regarding the use of combination anesthesia in liver resection surgery, due to the probable coagulopathy^[4] that accompanies procedures of this kind, and its complications (*e.g.*, spinal hematoma). The anesthetist therefore must weigh the advantages of the epidural catheter against the possible complications associated with its placement and removal.

The present study examines the hemostatic changes in patients undergoing liver resection due to colorectal cancer metastases, their course, and whether the extent of liver resection is a predictor of postoperative coagulopathy.

Assessment is also made of intraoperative bleeding, associated respiratory complications, stay in critical care and time to hospital discharge according to the anesthetic technique used (general *vs* combination anesthesia).

MATERIALS AND METHODS

Following approval by the Ethics Committee, a prospective observational study was carried out involving 61 colorectal cancer patients undergoing surgery due to liver metastases in a tertiary hospital between January 2015 and June 2016. All patients gave their consent for inclusion in the study. In addition to demographic variables [age, gender and body mass index (BMI)], we recorded anesthetic risk, the patient medical history, previous continuous treatment with antiplatelet drugs or anticoagulants, preoperative hemostasis, type of liver resection (major, defined as the resection of ≥ 3 Couinaud segments, or minor, defined as the resection of ≤ 2 segments), type of anesthesia (general or combination anesthesia), intraoperative central venous pressure (CVP), hepatic vascular exclusion, surgery time, estimated blood loss, intra and postoperative blood products administered, weight of the surgical piece and hemostasis values at the end of surgery and after 24, 48, 72, 96 and 120 h. All surgeries were performed by the same surgical team with extensive experience in liver surgery. A first descriptive analysis was made of the preoperative variables, followed by an analysis of the behaviour of the postoperative hemostatic parameters over time.

Rocuronium was used as neuromuscular blocker in all patients, and sugammadex was used as reversal agent at the end of surgery where required.

Statistical analysis

The statistical analysis of the data was carried out using R Statistical Programming Language®-Project for Statistical Computing® version 2.15.0 for MS Windows XP® and Linux Fedora 16 Kernel 3.4.111^[5].

RESULTS

Of the total patients, 30 were subjected to general anesthesia and 31 to combination anesthesia (general anesthesia plus epidural analgesia).

There were no statistically significant differences between the groups in terms of the preoperative variables, with the exception of BMI (Table 1).

The international normalized ratio (INR) was analyzed at 0, 24, 48, 72, 96 and 120 h postsurgery (Table 2).

The maximum INR values were recorded between 24 and 48 h after surgery in both the general anesthesia and combined anesthesia groups, followed by a gradual decrease.

The type of surgical resection was seen to influence the behaviour of the INR values over time. Figure 1 shows the values recorded at 0, 24, 48, 72 and 120 h. In the case of major liver resection, the maximum INR value (recorded at 48 h postsurgery) was 1.54. The values subsequently decreased at 72 and 120 h (1.28 and 1.12, respectively). In the case of minor liver resection, the maximum INR value (likewise recorded at 48 h postsurgery) was 1.17. The values subsequently decreased at 72 and 120 h (1.06 and 1.01, respectively). The INR values showed statistically significant differences between major and minor resection. The mean INR curves were entered in a model including the type of resection and the type of anesthesia as INR determining factors (Figure 1).

The evolution of prothrombin activity (PA) was evaluated 0, 24, 48, 72 and 120 h postsurgery (Table 3).

Figure 2 shows the mean PA values according to the type of anesthesia and surgical resection performed. The behaviour of this parameter over time coincided with that of the INR values.

Considering the type of anesthesia and type of surgical resection, the mean blood losses were found to be 919 ml and 585 ml respectively for major and minor resection with combination anesthesia, and 1254 ml and 1116 ml respectively for major and minor resection with general anesthesia. The statistical analysis showed blood loss to be significantly related to the type of anesthesia ($P = 0.008$) and type of resection ($P = 0.016$).

Respiratory complications in turn were seen to be related to the type of anesthesia used ($P = 0.003$). The patients subjected to combination anesthesia suffered fewer postoperative respiratory complications (6.6%) than the patients subjected to general anesthesia (38%). Similarly, the incidence of complications was greater in the major resection group (27.3%) than in the minor resection group (17.9%) ($P < 0.01$).

The time from the end of surgery to gastrointestinal tolerance was related to the type of anesthesia administered: 60.4 h in the case of combination anesthesia *vs* 83.5 h in the case of general anesthesia ($P = 0.001$).

The mean time to discharge from critical care was 2.77 da and 3.74 d in the case of

Table 1 Demographic and preoperative data of the study series

	Combination (SD) n = 30	General (SD) n = 31	P-value
AGE	61.7 ± 9.9	63.6 ± 9.7	0.520
BMI	24.2 ± 3.01	26.1 ± 3.3	0.111
Mean blood Pressure	91.3 ± 12.8	95.2 ± 15	0.276
Creatinine	0.86 ± 0.31	0.80 ± 0.27	0.427
Glucose	108.9 ± 24.3	103.9 ± 18.9	0.344
Hemoglobin	12.9 ± 1.51	13.2 ± 1.85	0.568
Hematocrit	38.8 ± 4.42	39.1 ± 5.33	0.817
Platelets	222 ± 77.2	220 ± 83.6	0.862
INR	0.97 ± 0.09	0.98 ± 0.10	0.885
PA	106.7 ± 17.6	105.1 ± 174.6	0.817
aPTT	29.1 ± 2.32	29.3 ± 2.73	0.976

BMI: Body mass index; PA: Prothrombin activity; aPTT: Activated partial thromboplastin time; INR: International normalized ratio; SD: Standard deviation.

combination and general anesthesia, respectively, and 4.06 d and 2.32 d in the case of major and minor resection, respectively. The statistical analysis showed the number of days to discharge from critical care to be significantly associated to the type of resection ($P = 0.001$) but not to the type of anesthesia ($P = 0.069$).

In turn, the mean time to patient discharge home was 10.53 d and 7.62 d respectively for major and minor resection with combination anesthesia, and 10.47 d and 10.07 d respectively for major and minor resection with general anesthesia. The number of days to discharge was not significantly related to the type of resection ($P = 0.060$) or the type of anesthesia ($P = 0.129$). Interaction of the type of resection with the type of anesthesia yielded a pvalue close to statistical significance ($P = 0.052$).

DISCUSSION

Epidural analgesia is an accepted procedure in major abdominal surgery^[6]. Controversy regarding its use in liver surgery is due to the risk of postoperative coagulation disorders^[7,9], with spinal hematoma being the most feared complication, even in patients with normal preoperative coagulation parameters^[10,11]. The possibility of coagulation disorders after liver surgery and of an increased risk of bleeding complications requires the anesthetist to weigh the advantages of placing an epidural catheter against the possible complications of catheter placement and removal^[12].

The extent of liver resection, bleeding, and the functional capacity of the remaining liver tissue can affect the magnitude and duration of the postoperative coagulation disorders, and make the appropriate timing of epidural catheter removal an important issue^[13]. In coincidence with the literature, our protocol considers that an INR value of 1.55 should not be exceeded either in performing the epidural technique or in catheter removal^[14], and that a minimum prothrombin activity (PA) value of 60% should be observed^[15]. Other authors further lower PA to 50%^[16] and INR to 1.4^[17]. Stamenkovic *et al*^[12] established a maximum INR value of 1.2 for any type of resection.

Because of this controversy, many studies involving particularly live donors and liver resection procedures in general have evaluated the course of hemostasis after liver resection surgery. Most of them^[7,12-15] reported normal hemostatic control values by the fifth postoperative day. This is the reason why followup in our study was extended to the fifth day after surgery. Although, we recorded alterations in hemostasis, they proved transient, with maximum levels between 24 and 48 h after resection surgery. Our findings in this regard are consistent with those of Kim *et al*^[14] and Siniscalchi *et al*^[15].

In all but two cases, the hemostatic controls performed after 72 h showed the parameters to be below the normal values for removing the epidural catheter. The mentioned two patients had an epidural catheter, and the parameters were seen to have normalized 120 h after surgery, thus allowing catheter removal without complications.

The literature recommends the transfusion of fresh frozen plasma when epidural catheter removal proves mandatory and the hemostatic parameters have not been normalized^[7,12,16]. None of our patients required the transfusion of this blood product,

Table 2 International normalized ratio according to the type of anesthesia and type of resection

Time	Anesthesia	Resection	Mean	St. error	SD
0	Combi	Major	1.217	0.032	0.130
24	Combi	Major	1.516	0.053	0.219
48	Combi	Major	1.556	0.074	0.303
72	Combi	Major	1.265	0.042	0.173
120	Combi	Major	1.062	0.028	0.115
0	General	Major	1.207	0.035	0.134
24	General	Major	1.425	0.074	0.287
48	General	Major	1.542	0.099	0.385
72	General	Major	1.287	0.063	0.246
120	General	Major	1.124	0.052	0.203
0	Combi	Minor	1.048	0.049	0.154
24	Combi	Minor	1.171	0.057	0.182
48	Combi	Minor	1.160	0.098	0.309
72	Combi	Minor	1.065	0.074	0.233
120	Combi	Minor	0.979	0.048	0.153
0	General	Minor	1.142	0.121	0.271
24	General	Minor	1.220	0.027	0.060
48	General	Minor	1.174	0.078	0.175
72	General	Minor	1.040	0.071	0.160
120	General	Minor	1.018	0.088	0.197

Combi: Combined anesthesia; General: General anesthesia; SD: Standart deviation.

though Stamenkovic *et al*^[12] had to perform such transfusion in a patient with an INR value of 1.5 on day four after surgery.

Possible factors underlying such coagulopathy after liver resection have been described^[17], including the extent of resection, intraoperative bleeding and the functional capacity of the remaining liver tissue^[12,18]. In our study, statistically significant differences were observed directly relating the type of liver resection to the subsequent development of hemostatic alterations, in coincidence with the findings of Matot *et al*^[7] and Stamenkovic *et al*^[12].

Liver surgery involves a high risk of intraoperative bleeding due to the anatomical characteristics of the liver, and consequently there is a greater potential need for transfusion, and higher patient morbidity and mortality^[19].

Only a limited number of studies have contrasted surgical bleeding according to the type of anesthesia used. One such study was published by Page *et al*^[20], involving patients undergoing liver resection due to any disease condition. One of the study variables was blood loss, and comparison of the epidural analgesia group (mean 709 mL) *vs* the nonepidural group (mean 780 mL) revealed no significant differences. Likewise, Revie *et al*^[21], in their twoyear study of 177 patients undergoing liver resection due to any disease condition, recorded no significant differences in intraoperative bleeding according to the type of anesthesia used. In contrast to the above authors, our results indicate a mean intraoperative blood loss of 769 mL for combination anesthesia *vs* 1200 mL for general anesthesia the difference being statistically significant. However, since the aforementioned studies involved heterogeneous patient series, any comparative analysis entails a certain risk of bias.

Considering the characteristics of analgesia achieved with local anesthetics administered *via* the epidural route *vs* analgesia with intravenous opiates, such as possible block or attenuation of the entry of pain stimuli to the central nervous system, the literature indicates that epidural analgesia offers benefits in relation to postoperative respiratory morbidity with improved lung function and tissue oxygenation^[22]. Pöpping *et al*^[23] conducted a metaanalysis involving 58 studies with 5904 patients, of which 19 with 3504 patients analyzed respiratory complications. The authors concluded that the use of epidural analgesia was significantly associated to a decreased risk of postoperative pneumonia this being consistent with our own observations. Our study showed that 38.8% of the patients subjected to general anesthesia had some type of respiratory complication after surgery (pleural effusion, atelectasis, pneumonia), *vs* only 6.6% of those subjected to combination anesthesia.

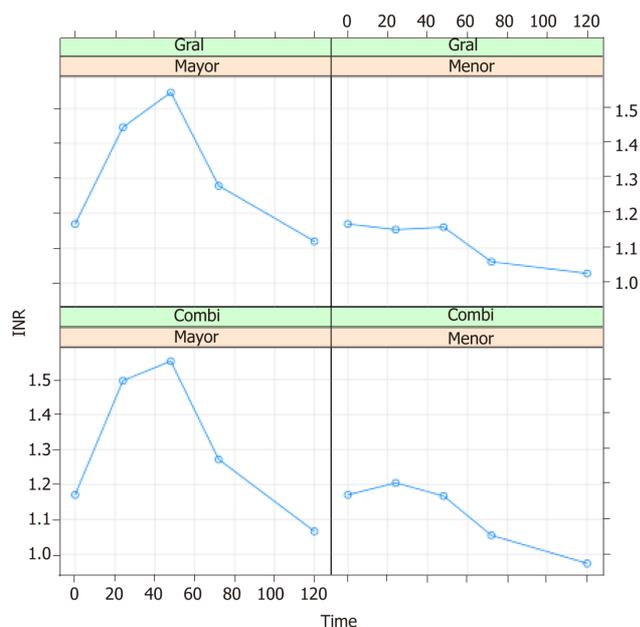


Figure 1 International normalized ratio according to the type of resection, type of anesthesia and time.

However, in the only identified study reporting results different from our own, Page *et al*^[20] described a greater number of respiratory complications (without specifying which) in their patients subjected to liver resection under epidural *vs* nonepidural analgesia though the differences were not significant.

Postoperative ileus implies a delay in the resumption of oral food intake and thus prolongs hospital stay^[24]. One of the main factors conditioning the accelerated recovery of intestinal function after abdominal surgery is the use of epidural analgesia^[25]. Studies similar to our own, such as those published by Ahmed *et al*^[26] and Hendry *et al*^[27], evaluating the application of a fasttrack program in liver surgery, have found gastrointestinal tolerance in all patients to be resumed 4872 h after surgery, in coincidence with our own findings. In our series, of the same size as those of Ahmed *et al*^[26] and Hendry *et al*^[27], the time to gastrointestinal tolerance was found to be 60.4 h on average in the combination anesthesia group *vs* 83.5 h in the general anesthesia group the difference being statistically significant. Our findings are likewise consistent with those of Qi *et al*^[28], who analyzed the outcomes of fasttrack liver surgery and observed a significant decrease in the time to tolerance (64 ± 17.9 h with fasttrack surgery *vs* 77.0 ± 26.4 h with the classical protocol).

Abu Hilal *et al*^[29] published one of the few studies referred to liver surgery in which patient stay in critical care was analysed. Without mentioning the type of anesthesia used, these authors compared laparoscopic surgery *vs* open surgery. The mean stay in the case of open surgery was about four days, which is longer than in our study. Chhibber *et al*^[30] in turn reported a threeday stay in critical care.

Our own findings were 3.7 d of stay on average in the general anesthesia group *vs* 2.7 d in the combination anesthesia group this indicating a tendency towards shorter stay in the latter group, though statistical significance was not reached ($P = 0.060$). However, on considering the type of liver resection performed (*i.e.*, major or minor), patient stay in critical care was seen to be significantly shorter in the minor resection group, with 2.3 d on average *vs* 4.3 d among the patients subjected to major liver resection.

Lastly, with regard to patient discharge home, Enhanced Recovery After Surgery protocols in liver surgery have been found to shorten the mean time to discharge (Pöpping *et al*^[23], Hendry *et al*^[27] Savikko *et al*^[31]). However, although we found combination anesthesia to result in a small reduction in time to discharge (9.3 d *vs* 10.3 d in the comparator group), the difference was not statistically significant. In any case, our stays were far longer than those recently published by Schultz *et al*^[32]. These authors, after making changes to a successful protocol already implemented in 2011^[2], including the administration of high dose corticosteroids before surgery (125 mg of methylprednisolone), recorded a median stay of two days for laparoscopic surgery *vs* four days in the case of open surgery.

In conclusion, epidural catheter placement and combination anesthesia constitute a safe alternative in patients undergoing liver resection due to colorectal cancer metastases. The coagulation alterations reach maximum levels at 24 and 48 h, with

Table 3 Evolution of prothrombin activity over time according to the type of anesthesia and type of resection

Time	Anesthesia	Resection	Mean	St. error	SD
0	Combi	Major	76.529	2.154	8.882
24	Combi	Major	58.824	2.661	10.973
48	Combi	Major	59.529	3.245	13.380
72	Combi	Major	76.353	3.240	13.360
120	Combi	Major	95.118	2.724	11.230
0	General	Major	78.133	3.275	12.682
24	General	Major	65.333	5.123	19.841
48	General	Major	60.200	5.206	20.164
72	General	Major	74.467	5.130	19.867
120	General	Major	87.533	4.916	19.041
0	Combi	Minor	95.800	5.781	18.281
24	Combi	Minor	81.600	5.053	15.981
48	Combi	Minor	82.500	5.905	18.674
72	Combi	Minor	94.000	7.335	23.195
120	Combi	Minor	101.600	4.960	15.686
0	General	Minor	88.800	8.540	19.097
24	General	Minor	75.000	2.408	5.385
48	General	Minor	79.000	6.716	15.017
72	General	Minor	92.800	9.019	20.167
120	General	Minor	99.000	9.555	21.366

Combi: Combined anesthesia; General: General anesthesia; SD: Standard deviation.

normalization of the parameters in all cases at 120 h after surgery. Statistically significant differences were observed in the evolution of the hemostatic parameters over time according to the type of liver resection involved. None of our patients required the transfusion of fresh frozen plasma for epidural catheter removal. There were no complications related to catheter placement.

There was less intraoperative bleeding in the combination anesthesia group. These patients moreover suffered fewer respiratory complications and showed a shorter time to oral tolerance.

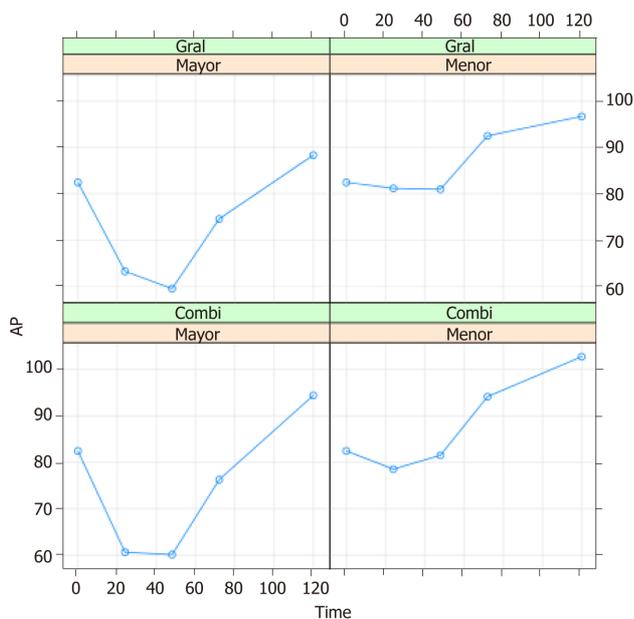


Figure 2 Prothrombin activity according to the type of anesthesia and type of resection.

ARTICLE HIGHLIGHTS

Research background

Epidural analgesia is a well-known technique use in thoracic and abdominal surgery for its benefits in stress response, pulmonary complications. Anesthesiologists are afraid of its use in patients with potentially haemostatics disorders. Liver surgery is an example of them. In literature is well described the use of epidural analgesia in hepatic surgery and others, with different opinions. So that, we wanted to study the behaviour haemostatic profile after a particular etiology of hepatic resection, colon-rectum liver metastases. We think are patients with particular peculiarities in liver function non comparable to others disease, thus the use of epidural analgesia could be safer than in others, with greater benefits than risks.

Research motivation

Patient wellness, patient comfort, patient care, minimize patient stress previous and following days after surgery is one of the goals for all health professionals. So that, in literature is well published the benefits of epidural analgesia in many patients under thoracic or abdominal surgeries. Is for that we started this study, because of the discrepancies existing in use or not use epidural techniques in patients under liver surgery with potentially haemostatic postoperative disorders.

Research objectives

To know the behaviour of haemostatic profile following a colon-rectum metastases liver resection, to considerer if benefits of epidural analgesia are greater than risks.

Research methods

The research methods (*e.g.*, experiments, data analysis, surveys, and clinical trials) that were adopted to realize the objectives, as well as the characteristics and novelty of these research methods, should be described in detail.

Research results

We found in both minor and major hepatic resections, there was oscillation in international normalized ratio (INR) and prothrombin time till 48th postoperative hours. These variations in minor resections were never greater than INR 1.5, instead in major resections existed at 48th postoperative hours haemostatic alteration that turn to normal range before postoperative day 5. We did not use fresh frozen plasma or prothrombin complex to improve the haemostasia prior to remove an epidural catheter.

Research conclusions

Haemostatic profile following colon-rectum hepatic metastases resection. Safety use an epidural catheter in patients under colon-rectum liver metastases resection. Benefits of epidural analgesia for patients under colon-rectum metastases liver resections are greater than risks, but if you chose use it, use it with care. Offer to anaesthesiologists another tool in anesthesia and analgesia management in patients with those characteristics.

Research perspectives

Never is enough when in terms of health recommendations is worked. More studies are always necessary to improve and certified your studies.

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