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Comparison between low- versus high-dose intrathecal morphine in lumbar spine surgery to control postoperative pain

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Abbreviations list

ASA	American Society of Anesthesiologists
VAS	Visual analog scale
FDA	Food and Drug Administration
CSF	Cerebrospinal fluid
MS	Morphine sulfate

SUMMARY

Introduction: Intrathecal opioids provide a quite satisfactory postoperational analgesia, and it is estimated that they are effective in controlling acute pain within the first 24 hours after surgery. **Material and methods:** An experimental, comparative, randomized, and double-blinded study was carried out to compare the effectiveness of low doses against high doses of intrathecal morphine sulfate to handle post operational pain in patients who underwent lumbar-sacra surgery; in addition, pain, nausea and vomit were evaluated. Eighty seven patients were included, distributed randomly in two groups, one with 44 patients and the other with 43. One group was given intrathecal morphine sulfate (200 µg) and bupivacaine (15 µg) at 0.375%. The other group was given morphine sulfate (500 µg) and bupivacaine (15 µg) at 0.375%; both groups were also given balanced general anesthesia. Additionally, patients received ondansetron (8 mg) intravenously. **Results:** There was no significant difference in statistical terms as to pain and rash in both groups. There was a significant difference six hours after surgery as to postoperational nausea and vomit, being more frequent in the group that was given 500 µg of morphine. Besides, there was a higher frequency of collateral effects such as urinary retention in the group of the higher dose; the other group showed postpuncture headaches. No cases were registered of respiratory depression. Complications were easily controlled and none jeopardized any patient's life. None of the rash cases required further treatment. **Conclusions:** Low doses of morphine sulfate are safe and effective in postoperational analgesic in surgery of the lumbar-sacral spine, with a lower incidence of contrary effects.

Key words: Intrathecal morphine, spinal lumbo-sacral surgery.

RESUMEN

Introducción: *Los opioides intratecales proveen una muy satisfactoria analgesia postoperatoria y se estima que es efectiva en el control agudo del dolor en las primeras 24 horas después de cirugía.* ***Material y métodos:*** *Se realizó un estudio experimental, comparativo, aleatorizado y doble ciego para comparar la eficacia de dosis bajas contra altas de sulfato de morfina intratecal para manejo del dolor postoperatorio en pacientes sometidos a cirugía lumbosacra, además se valoró dolor, náusea y vómito. Se incluyeron 87 pacientes, que se distribuyeron aleatoriamente en dos grupos, de 44 y 43 pacientes cada uno. A un grupo se le administró intratecalmente sulfato de morfina 200 µg y bupivacaína 15 µg al 0.375% y al otro sulfato de morfina 500 µg y bupivacaína 15 mg al 0.375%, además de anestesia general balanceada a ambos grupos. Los pacientes adicionalmente recibieron ondansetron 8 mg endovenosa.* ***Resulta-***

dos: *No existió diferencia estadísticamente significativa en cuanto a dolor y prurito en ambos grupos. Existió diferencia significativa a las 6 horas con respecto a náusea y vómito postoperatorio, siendo mayor la frecuencia en el grupo de 500 µg de morfina. Se observó mayor frecuencia de efectos colaterales como retención urinaria en el grupo de 500 µg y cefalea postpunción en el grupo de 200 µg. No se registraron casos de depresión respiratoria. Las complicaciones fueron fácilmente controladas y no hubo ninguna que pusiera en peligro la vida. Ningún caso de prurito requirió tratamiento.* ***Conclusiones:*** *Dosis pequeñas de sulfato de morfina son efectivas y seguras para analgesia postoperatoria en cirugía de columna lumbosacra, con una incidencia menor de efectos adversos.*

Palabras clave: *Morfina intratecal, cirugía de columna lumbosacra.*

INTRODUCTION

It is well known that opioids such as morphine exert their effects by mimicing natural substances called endogenous opioid peptides or endorphins. Moreover it is very much known about the basic biological aspects of the endogenous opioid system and its biochemical and molecular complexity, diversity and widespread anatomy[1]. Intrathecal opioids provide a very satisfactory postoperative analgesia and is believed to be effective in over 85% in the control of acute pain in the first 24 hours after surgery[2].

BACKGROUND

The first unquestionable reference to opium is in the Theophrastus' writings in the third century BC. Arab physicians were well versed in the uses of opium, the Arab merchants introduced the drug to the Orient, where it was used mainly for control of dysenteries. During the Middle Age, many people appreciated the uses of opium. In 1680 Sydenham wrote: "Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium[1]."

More than a century has passed since that August Bier first described the intrathecal administration of cocaine to "maintain most of body insensitive to pain for surgical purposes", has since obtained considerable experience and knowledge of physiology, pharmacology and clinical application of intrathecal anesthesia[3].

In 1979, Behar et al and Wang et al first reported the use of epidural and intrathecal opioids for the management of acute postoperative pain[4,5].

In 1999, Gwirtz et al noted in about 6000 patients over a period of 7 years that intrathecal opioid analgesia was controlling postoperative pain adequately with a high degree of patient satisfaction and a low incidence of side effects and complications[2].

OVERALL

Although exact descriptions of the spinal canal anatomy are available from the nineteenth and early twentieth centuries, the use of modern radiological imaging technology has provided some evidence of important anatomical and pathophysiological new aspects in intrathecal anesthesia. The spinal cord lies within the vertebral canal and is surrounded by pia mater, a highly vascularized membranous layer closely covering the spinal cord and brain. The outermost layer is the dura mater and the one innermost is the pia mater. Between these two layers is the arachnoid, which a delicate avascular membrane that is attached to the dura mater. The arachnoid currently represents the most important and active barrier, outlining the region of interest for intrathecal anesthesia (subarachnoid space). It comprises 2 portions: a laminar and compact portion covering the inner surface of the dural sac and a trabecular portion that extends like a web around the pia mater. The arachnoid is not only a passive container of cerebrospinal fluid but is actively involved in the transport of anesthetics and neurotransmitters that are involved in the spinal block[3]. The subdural space contains the spinal nerves, spinal cord and cerebrospinal fluid (CSF). The CSF is a crucial factor that determines the effects of intrathecally administrated agents, because all drugs injected into the subarachnoid space are diluted in the CSF before reaching the effector site in the spinal cord.

There is a considerable interindividual variation in total volume of CSF, demonstrated by magnetic resonance, with lumbosacral CSF volumes ranging from 28 to 81 milliliters. The lumbosacral CSF volume is the most important factor affecting the peak sensory block and duration of spinal anesthesia. Although there is some correlation between body size and CSF volume, the volume can not be estimated reliably with simple anthropometric characteristics. However, these findings support the clinical evidence that the application of intrathecal anesthesia is mainly determined by the amount of local anesthetic solution injected into the sub-

arachnoid space. Conversely, if the total dose is kept constant, the volume and concentration of the injected drug has no substantial clinical significance on the characteristics of the blockade, including the total dose injected influences on the minimal effective concentration of local anesthetic required to produce surgical anesthesia[3].

Local anesthetic solutions work by creating conformational changes in the neuron´s voltage-gated sodium channels, which reduces, or completely blocks, the flow of sodium ions through these channels. This, in turn, prevents nerve impulses from being conducted along the length of the axon. The traditional explanation for the nerve block created by intrathecal injection of local anesthetics is a complete block in the conduction of nerve impulses from the periphery to the supraspinal nucleus. However, it has been well established that the intrathecal injection of a local anesthetic also interferes with the function of other neurotransmitters such as Substance P or gamma aminobutyric acid (GABA). It has also been shown that spinal anesthesia produces sedation, which is related to the maximum level of consciousness achieved[3].

Intrathecal opiates can produce a marked and selective inhibition of the small A-delta and C-fibers, which are directly involved in the transmission of pain sensation signals. It has been shown that the addition of 0.1 – 0.2 mg of morphine to the intrathecal local anesthetic solution produces the greatest benefit in terms of improved pain control, together with the maximum decrease in the number and frequency of adverse reactions[3].

Due to its hydrophilic nature, morphine has increased potential for rostral migration in the cerebrospinal fluid (CSF), which may lead to delayed respiratory depression. Lipophilic opiates such as fentanyl and sufentanyl have a much quicker onset of action and little risk of causing respiratory depression. For that reason, they are used much more frequently to potentiate the nerve blocking effects of local anesthetic agents without prolonging the spinal block[3].

Morphine is the only opiate currently approved by the Food and Drug Administration (FDA) for intrathecal administration[6]. In recent years, low-dose intrathecal morphine has once again become very popular in postoperative anesthesia[7]. Low-dose intrathecal opiates are a safe, effective, and relatively inexpensive option in the routine management of acute, postoperative pain following a great number of different surgical procedures, including coronary artery surgery, major vascular surgery, hip replacement surgery, abdominal surgical procedures, cholecystectomy, obstetric surgery and normal vaginal deliveries[8].

Morphine is also a good choice as a neuraxial opiate, since the duration of action of the lipophilic opiates (sufentanyl and fentanyl) is short, usually 1 to 6 hours, compared to morphine´s effect,which lasts approximately 24 hours. When administered intrathecally, morphine´s peak anesthetic effect occurs between 4 and 7 hours after administration, and thus preoperative administration produces maximum analgesia during the postoperative period.

One of the advantages of the intrathecal route of administration is cost-reduction, since intrathecal opiates cost less than one third of what the epidural opiates cost. Epidural opiate administration requires the use of more expensive equipment, in addition to the materials needed for its infusion (the cost of the medication, infusion pumps, trained personnel, and proper care while the patient is undergoing treatment).

In order to achieve adequate postoperative anesthesia, and reduce the length of the hospital stay, the combined use of local anesthetics, nonsteroidal anti-inflammatory drugs (NSAIDs) and opiates, has been proposed[7]. Combining fentanyl (lipid soluble, rapid onset of action) and morphine (water soluble, prolonged duration of action) synergistically with a small dose of bupivacaine, provides the dual benefits of a fast acting and prolonged anesthesia and it is common practice in many anesthesia centers[2].

A single dose of intrathecal morphine, administered at the time of the surgery, is easy to maintain and provides good neuraxial anesthesia during the first postoperative day, and it is a viable treatment option until such time as the patient is able to take more effective oral analgesics[2].

France and his team of researcers showed that 0.011 mg/kg of intrathecal morphine during lumbar spine surgery provides a safe and effective adjuvant for the management of postoperative pain.

The analgesia produced by intrathecal morphine is more than adequate for the relief of pain following many different types of surgery in doses ranging from 0.025 to 20 mg. A single dose is usually enough for postoperative analgesia, even following major orthopaedic procedures. However, doses greater than 0.5 – 1 mg are associated with a marked increase in adverse reactions, including respiratory depression. In an attempt to limit adverse reactions, using a low dose of opiates (approximately < 0.03 mg of intrathecal morphine) has been suggested[11].

Rathnell and his team concluded that low doses of intrathecal morphine, ranging from 0.1 to 0.3 mg, provide adequate analgesia and significantly decrease the amount of intravenous morphine that is needed during the first 24 hours following the surgery[11].

Motamed and colleagues suggest that a low dose of spinal morphine combined with a low dose of bupivacaine can be a simple and trustworthy component of a multimodal approach to surgical anesthesia[7]. Furthermore, intrathecal morphine has also been shown to reduce the amount of blood that is lost during spinal surgery[11].

ADVERSE REACTIONS

The most dreaded complication associated with the intrathecal administration of morphine is respiratory depression, with an incidence of 3%; but it is noteworthy that all patients who experience respiratory depression respond to an infusion of naloxone, without reverting the analgesia[2].

Although intrathecal morphine is undoubtedly effective in relieving postoperative pain associated with major surgical procedures of the spinal column, the risk of developing respiratory depression is significant, and appears to be dose-related. The analgesic effect is also related to the dose, whereas nausea, vomiting, pruritus, and urinary rentention are not.

Nausea and vomiting (25%) are adverse reactions which were reported, but which also normally respond favourable to the more traditional treament interventions.

Pruritus is the most common adverse reaction following intrathecal administration of morphine, with a reported incidence between 62 and 94%[13].

Gwirtz and co-workers showed that the incidence and severity of adverse reactions were acceptable and easily controlled, and there were no serious complications which jeopardized the lives of any of the participants[2].

Urinary retention is not dose-related, and as of yet, we have no way to predictably prevent patients from developing this condition[7].

METHOD

This was a comparative, randomized, double-blind, experimental study which evaluated 87 adult patients who had undergone surgery of the lumbrosacral spine. The inclusion criteria were as follows: 1. Age greater than 18 years, 2. Patients who had undergone spinal surgery, 3. Patients with a physical functional status of I or II, according to the American Society of Anesthesiologists (ASA). The patients were excluded for the following reasons: 1. Did not consent to the spinal anesthesia, 2. Pediatric-aged patients (0 to 17 years), 3. Patients who had spinal column surgery but not at the lumbrosacral level, 5. Patients with an ASA level of physical functioning either 0 or 5, 6. Infection at the infusion site, 7. Coagulopathy, 8. Metastatic disease in the spinal cord, 9. Allergy to any component of the intrathecal solution, 10. History of chronic opiate consumption, 11. Technical difficulties carrying out the procedure, 12. Hypersensitivity to bupivacaine and morphine sulfate, 13. History of pruritus and/or preoperative nausea. Also eliminated were patients who, upon completion of the study, continued to medicate with opiates, patients who reverted to naloxone or nalbufin upon completion of the surgery, and patients who, once the surgical procedure was completed, remained intubated.

The study was conducted after obtaining the approval of the Bioethics Committee of Hospital Central Militar, and informed consent was obtained from each patient, in writing. A total of 87 patients were evaluated, all of whom were scheduled for surgery of the lumbosacral spine. The patients were randomly assigned to one of two groups, A or B, with 44 and 43 patients, respectively. Patients in Group A received an intrathecal dose of bupivacaine (15 mg at 0.0375%) and 500 μg of morphine sulfate. Group B patients were given intrathecal bupivacaine (15 mg at 0.0375%) and 200 μg of morphine sulfate. Neither the surgeon, the nursing staff, the anesthesiologist, nor the patient himself knew what dose he received. All injections were diluted to a final volume of 4 ml with normal saline solution, and administered by the anesthesiologist usinga 25- and 26-gauge spinal needle, prior to the start of the surgery.

Anesthesia management was standard for all patients, and included anti-anxiety premedication; induction with propofol, vecuronium and fentanyl; maintenance anesthesia with isofluorane in oxygen. Monitoring during the procedure was also standard. Near ideal surgical conditions were achieved and sustained by employing extra medication to maintain the hemodynamic status of the patient.

Following the surgery, the patients were transferred to the postoperative care unit (PCU). When the patients met the criteria for leaving the PCU, they were transferred back to their respective units. The time of arrival at the PCU was designated as Time Zero, and the evaluations to determine pain, pruritus and nausea were performed every 6 hours, until 24 and 48 hours. Rescue analgesia was prescribed on an "as-needed" basis, and consisted of 30 mg of ketorolac IV, alternated with 1 g of metamizole IV every 8 hours.

Postoperative pain was quantified using the Visual Analog Scale (VAS) with a range of 0 to 10 cm. The degree of pruritus and nausea was classified as 0 = none, 1 = mild, 2 = moderate, 3 = severe and 4 = very severe. Pruritus was defined as the sensation which produces the urge to scratch.

The lead investigator conducted the data collection in formats designed specifically for this purpose, and was also in charge of data analysis. The capture and coding of data was done on electronic pages in Excel 2003 of Microsoft Windows. The variables were then compared using SPSS versión 10.0 and Sigmastat version 2.0. One way analysis of variance (ANOVA) was used in the case of numeric variables. In all analyses, statistical significance was defined as $p < 0.05$.

RESULTS

Between March and September of 2006, 89 patients enrolled in the study, 2 of whom were later excluded when they had to be intubated and transfered to the ICU. Therefore, a total

of 87 patients completed the study, 44 in Group A and 43 in Group B.

Demographic and intraoperative characteristics such as gender, age, weight, total dose of IV fentanyl, ASA risk and duration of surgery are shown in Table I. No significant differences were found, either in demographic or intraoperative characteristics, between the two groups. A distribution by diagnosis and by type of surgery within each group is depicted in Table II. No difference was found between the two groups in terms of diagnostic categories or type of surgery. The two groups did differ significantly, however, with respect to the frequency and percentage of spinal headaches and urinary retention (Table III). The incidence of spinal headache was 9.1% and that of urinary retention was 4.5%. No patient suffered respiratory depression during the course of the study.

There was a statistically significant difference in the incidence of nausea and vomiting between the two groups at hour 6 (see Table IV) but not at hours 0, 12, 18, 24 or 48. No difference was found in the incidence of pruritus, and no patient in either group required anti-pruritic medication (see Table V). Both groups were also very similar with respect to the average total score on the visual analog scale for pain, with no significant differences between the two groups (Table VI).

DISCUSSION

The management of postoperative pain through the administration of a single dose of intrathecal opiates is a practice which has gained a large following. Early studies, like the one from Wang et al.[15] where intrathecal morphine (in doses ranging from 500 µg to 1 mg) was used for postoperative pain management in cancer patients, showed effective analgesia for up to 22 hours without respiratory depression or excessive drowsiness. However, other authors have reported a high incidence of respiratory depression, but that was generally with high doses (2 – 15 mg))[16]. More recent studies have suggested that "mini-doses" of

Table I. Demographic and intraoperatory date.

	Bupivacaine 15 mg at 0.375% + SM 500 µg (n = 44)	Bupivacaine 15 mg at 0.375% + SM 200 µg (n = 43)
Sex (f/m)	17/27	23/20
Age (years)	29/81/51.4/15.01	22/81/48.7/16.49
Weight (kg)	54/94/70.25/9.36	50/96/68.9/10.02
Fentanyl IV total doses (µg)	250/1300/459/210	200/1500/447.9/253.5
ASA (I/II)	32/12	34/9
Surgical time (h:min)	02:10/12:00/05:22/02:26	01:37/12/25/04:26/02:11

Value in minimum, maximum, average and standard deviation.

Table II. Diagnosis and type of surgery.

	Bupivacaine 15 mg at 0.375% + SM 500 µg (n = 44)	Bupivacaine 15 mg at 0.375% + SM 200 µg (n = 43)
Diagnosis		
Hernia of disc	13 (29.5)	18 (41.9)
Radicular compression	13 (29.5)	13 (30.2)
Narrow lumbar channel	6 (13.6)	6 (14.0)
Espondilolistesis	7 (13.9)	4 (9.3)
Others	5 (11.4)	2 (4.7)
Surgery		
Discectomy	7 (15.9)	16 (37.2)
Radicular liberation	11 (25.0)	11 (25.6)
Instrumentation	22 (50.0)	15 (34.9)
Others	4 (9.1)	1 (2.3)

Information appears in number of cases and in brackets the percentage.

Table III. Frequency and percentage of migraine postpuncture and urinary retention.

	Bupivacaine 15 mg at 0.375% + SM 500 µg (n = 44)	Bupivacaine 15 mg at 0.375% + SM 200 µg (n = 43)
Urinary retention	3 (6.8)	1 (2.3)
Migraine postpuncture	3 (6.8)	5 (11.6)

Information appears in number of cases and in brackets the percentage.

Table IV. Incident of nausea and postoperatory vomit.

Nausea and vomit PO	0 hours p = 0.067	6 hours p = 0.038	12 hours p = 0.111	18 hours p = 0.067	24 hours p = 0.333	48 hours p = 0.333
Null	23/53.5	21/48.8	34/79.1	38/88.4	40/93.0	41/95.3
	29/65.9	34/77.3	36/81.8	41/93.2	42/95.5	44/100
Slight	14/32.6	12/27.9	3/7.0	3/7.0	3/7.0	1/2.3
	14/31.8	7/15.9	6/13.6	2/4.6	2/4.5	0/0
Moderate	4/9.3	6/14.0	5/11.6	2/4.7	0/0	1/ 2.3
	0/0	3/6.8	1/2.3	1/2.3	0/0	0/0
Severe	2/4.7	4/9.3	1/2.3	0/0	0/0	0/0
	1/2.3	0/0	0/0	0/0	0/0	0/0
Very severe	0/0	0/0	0/0	0/0	0/0	0/0
	0/0	0/0	1/2.3	0/0	0/0	0/0

Information appears in number of cases and later the percentage.

Table V. Incident of pruritus in both groups.

Prurito	0 hours p = 0.391	6 hours p = 0.204	12 hours p = 0.200	18 hours p = 0.067	24 hours p = 0.432	48 hours p = 0.672
Null	24/55.8	21/48.8	23/53.5	25/58.1	34/79.1	40/93.0
	23/52.3	21/47.7	20/45.5	28/63.6	35/79.5	42/95.5
Slight	15/34.9	18/41.9	17/39.5	14/32.6	9/20.9	3/7.0
	17/38.6	19/43.2	23/52.3	15/34.1	9/20.5	2/4.5
Moderate	3/7.0	3/7.0	3/7.0	4/9.3	0/0	0/0
	4/9.1	3/6.8	1/2.3	1/2.3	0/0	0/0
Severe	1/2.3	1/2.3	0/0	0/0	0/0	0/0
	0/0	1/2.3	0/0	0/0	0/0	0/0
Very severe	0/0	0/0	0/0	0/0	0/0	0/0
	0/0	0/0	0/0	0/0	0/0	0/0

Information appears in number of cases and later the percentage.

morphine (< 100 µg) provide adequate analgesia with very few adverse reactions such as respiratory depression, nausea, vomiting, and urinary retention[17]. These results may imply that the complications seen with intrathecal morphine in the early studies could have more to do with the higher doses of morphine used than with the route of administration[2]. Based on the results from large scale studies, the authors of the present study suggest that intrathecal opiates can be used safely in the same context as peridural opiates[2].

The most dreaded complication associated with the intrathecal administration of opiates is respiratory depression, yet in the present study, not one patient developed this adverse reaction. It should also be noted that naloxone can

Table VI. Average values of visual analogue pain scale.

Hours	Bupivacaine 15 mg at 0.375% + SM 500 µg (n = 44)	Bupivacaine 15 mg at 0.375% + SM 200 µg (n = 43)
0	0.65	1.30
6	1.20	1.30
12	0.88	1.23
18	1.38	1.86
24	1.61	2.37
48	1.34	2.16

Values are the average of the visual analogous scale from 0 to 10. Value of p = 0.324

reverse the respiratory depression without affecting the analgesia[2].

Pruritus is the most frequent negative side effect (incidence 62 – 94%)[2], and although the underlying mechanism of action is not clear, it appears to be mediated by the interaction of morphine with 5-hydroxitriptamine receptors. Nausea and vomiting are common adverse reactions due to morphine´s stimulation of the trigger zone in the area postrema. All patients were given an 8 mg dose of ondansetron as prevention. This study found no difference between the two treatment groups with respect to the frequency or the intensity of pruritus, which suggests that this symptom is not dose-dependent, although the use of ondansetron has been reported to decrease the incidence of pruritus(48-70%)[2].

As far as nausea and vomiting 6 hours after arriving at the recovery room, there was a statistically significant difference between the two groups, with the 500 µg group experiencing much more nausea and vomiting. This would indicate that the higher the dose of morphine, the higher the incidence of postoperative nausea and vomiting.

The evidence is not clear on whether intrathecal morphine can actually protect agaisnt developing spinal headaches, although fentanyl has been associated with a lower incidence of spinal headhaches[18].

In this study, we found a spinal headache frequency of 9.1%, which correlates with the incidence reported previously by Pan et al[19]. The frequency in the 500 µg group was 6.8% and the frequency in the 200 µg was 11.6%. So, even though this study was not designed to evaluate spinal headaches, it is interesting to note that there was no significant difference between the two groups.

Both the incidence and the severity of side effect complications were aceptable and easily managed, and there was no adverse reaction which jeopardized a patient´s life.

We found that morphine is effective for postoperative pain management in lumbosacral spine surgery, independent of the dose administered, and that it provides a good level of analgesia during the first 48 hours following the surgery.

This study also showed an increased incidence in urine retention in the 500 µg group *versus* the 200 µg group, suggesting that this side effect may, in fact, be dose related, and that lower doses may be safer in patients where renal function is a consideration.

CONCLUSIONS

Using a combination of morphine sulfate and bupivacaine as a solution for intrathecal anesthesia is an effective option for the management of postoperative surgical pain, given that it is significantly less expensive than peridural anesthesia, its relatively easy to apply, it only requires a single dose, and is more comfortable for the patient. In addition, this drastically reduces hospital costs since the use of rescue analgesia is also reduced; without pain the patient is more likely to go home sooner (patient satisfaction is another important factor which we observed in this study).

The low-dose option is safe, effective, and relatively cheap, and has a low incidence.

We also noted that the loss of blood during the surgery decreases with the use of combined anesthesia

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