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Comparison of the effects of thoracic and lumbar epidural anaesthesia on induction and maintenance doses of propofol during total i.v. anaesthesia

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Background. In this randomized, double-blind study, the effects of thoracic and lumbar epidural anaesthesia on the induction doses (IDs) and maintenance doses (MDs) of propofol during bispectral index (BIS) guided total i.v. anaesthesia were compared.

Methods. Fifty-four patients (three groups, $n=18$ each) undergoing urological surgery in lumbotomy position were studied in Groups T (Th7–8) and L (L3–4), epidural anaesthesia was performed with initial doses obtaining sensorial block at Th4 (SD 1) followed by 7 ml h^{-1} infusion; Group C received no epidural anaesthesia intraoperatively. The ID (BIS <45) and MD (BIS: 40–50) of propofol and recovery (BIS >80) and extubation times were recorded.

Results. The volume to obtain a block was significantly lower in Group T than in Group L [10.7 (1.5) *vs* 14.7 (1.0) ml; $P<0.001$]. ID was significantly higher in Group C compared with that in Groups T and L [2.16 (0.15) *vs* 1.33 (0.19) *vs* 1.46 (0.14) mg kg^{-1}, respectively; $P<0.001$] with no significant difference between Groups T and L. For MD, there were significant differences between all groups [3.82 (0.9) *vs* 5.8 (1.32) *vs* 9.21 (0.55) mg kg^{-1} h^{-1} in Groups T, L, and C, respectively; $P<0.001$]. For recovery and extubation times, Group T<Group L<Group C [1.4 (0.5) *vs* 3.3 (1.2) *vs* 8.1 (0.99) min, respectively, $P<0.001$; and 3.4 (0.52) *vs* 5.8 (1.32) *vs* 11.4 (1.96) min, respectively; $P<0.0001$].

Conclusions. Similar segments blocked with epidural anaesthesia have resulted in similar ID. During maintenance, identical amounts of bupivacaine applied from different levels have resulted in different MD of propofol. The concentration of the epidural anaesthesia appears to play a more important role than the applied amount of the local anaesthetic.

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Combination of epidural and general anaesthesia is one of the anaesthetic strategies used for major surgery to reduce the requirements of general anaesthetics. Local anaesthetics have been demonstrated to reduce the doses of i.v. and inhalation anaesthetics after the administration via different ways such as epidural,[1–3] intrathecal,[4 5] and i.m.[6–8] However, the exact mechanism of this interaction remains unexplained; moreover, the magnitude of the decrease in general anaesthetic doses is also unknown, which can cause an unwarranted superficial or deep hypnotic component of anaesthesia.

The bispectral index (BIS), an EEG derivative, has been shown to be a reliable and sensitive monitor of the hypnotic component of anaesthesia.[9 10] BIS can be an objective help to determine whether and—if so—how much the doses of hypnotics have to be reduced after the local anaesthetic administration.

The mechanism of the interaction of epidural and general anaesthesia is still not clear, and it has still not been conclusively explained whether the systemic effects of applied local anaesthetic or the epidural anaesthesia are

the crucial factor. We hypothesized that the concentration of the epidural anaesthesia rather than the dose of the local anaesthetic plays a dominant role in the hypnotic effects of the epidural anaesthesia. In a randomized, double-blind study, we tested the effects of thoracic and lumbar epidural anaesthesia on the induction dose (ID) and maintenance dose (MD) of propofol during BIS-guided total i.v. anaesthesia (TIVA).

Methods

With patient informed consent and approval from the local Ethics Committee, we studied 54 ASA I or II patients undergoing urological surgery in lumbotomy position expected to last at least 1 h. To detect a decrease of 0.35 mg kg^{-1} of the ID of propofol (accepting an alpha error of 5% and a beta error of 10%), the required study size was 16 patients per group. Exclusion criteria were general contraindications for epidural anaesthesia, including patients' refusal, known hypersensitivity to the study drugs, preoperative analgesic and hypnotic usage, and any documented preoperative systemic disease, which can interfere with the epidural anaesthesia. Gender, age, weight, and height of the included patients were recorded.

Patients did not receive any premedication. They were prehydrated with 10 ml kg^{-1} of NaCl 0.9% solution, and routine monitoring was applied, including ECG, non-invasive arterial pressure, and pulse oximeter (Horizon 2000, Mennen Medical, Rehovot, Israel). BIS was monitored using a BIS sensor (BIS™ Sensor; Aspect™ Medical Systems, Inc., Newton, MA, USA) applied to the forehead as described by the manufacturer (A-2000 BIS™ monitor, System rev.2.1, Aspect™ Medical Systems, Inc., Norwood, MA, USA). Heart rate (HR), mean arterial pressure (MAP), oxygen saturation (Sp_{O_2}), and BIS were monitored throughout the procedure and the operation. BIS smoothing rate was set at 15 s.

Patients were then randomly allocated to one of three groups according to a sealed envelope technique in a double-blind manner. Before the intervention, all patients were sedated with i.v. midazolam 3 mg. In Group T (thoracic epidural) and Group C (Control) (n=18 each), an 18-gauge epidural catheter (B. Braun, Melsungen, Germany) was inserted through the Th7-8 intervertebral space by a midline approach with the loss-of-resistance technique and placed 3–4 cm in the cephalad direction. In Group L (lumbar epidural) (n=18), the same approach was used to insert an epidural catheter through the L3–4 intervertebral space. In all patients, the placement of the catheter was verified by 3 ml of 2% lidocaine+1/200 000 adrenaline.

Initially, 7 ml of bupivacaine 0.25% in saline+fentanyl 50 μg in Group T and 12 ml of bupivacaine 0.25% in saline+fentanyl 50 μg in Group L were administered to achieve a sensorial block (negative pin-prick) at Th4 at least 30 min before anaesthetic induction.

If the block has not reached Th4 after 15 min, additional doses (1 ml per segment) of a solution consisting of bupivacaine 0.25% plus Fentanyl 5 mg ml^{-1} in saline were administered. If the obtained block was higher than Th3 or lower than Th5 [Th4 (1) level] also after the additional doses, the patient was excluded. An infusion of the same solution (7 ml h^{-1}) was then started in Groups T and L before an induction of general anaesthesia and continued until the end of the operation. In Group C, no loading dose was applied after the test dose; and an epidural infusion of saline (7 ml h^{-1}) was started just before the induction of general anaesthesia and continued until the end of the operation.

After a bolus dose of fentanyl 2 μg kg^{-1} i.v., an anaesthetist, blinded to the applications performed earlier, injected propofol 10 mg (1 ml) in 5 s every 15 s until the BIS score was reduced to <45. The total dose of propofol required to achieve a BIS of <45 was recorded in milligram per kilogram (ID). When BIS value was <45, the response to verbal commands was evaluated. Tracheal intubation was accomplished after administration of rocuronium 0.7 mg kg^{-1}. Volume-controlled ventilation (Dräger SA2, Drägerwerk, Lübeck, Germany) was started with 9 ml kg^{-1} tidal volume and ventilatory frequency was adjusted to maintain endtidal carbon dioxide tension 30–35 mm Hg. Lungs were ventilated with 50% oxygen and 50% air.

After intubation, infusion of propofol 10 mg kg^{-1} h^{-1} was started. The dose of propofol was titrated to keep the BIS score between 40 and 50. When the BIS score was out of these limits for ≥10 s, the dose of propofol was changed by 1 mg kg^{-1} h^{-1} every 20 s. The total MD of propofol during the operation was recorded in milligram per kilogram per hour (MD). Additional doses of rocuronium 0.1 mg kg^{-1} were administered when necessary until skin closure.

Inadequate analgesia was defined as response to surgical stimuli by hypertension (SAP>20% above preoperative baseline value for >5 min) or tachycardia (HR>20% above preoperative baseline value), while BIS level was between 40 and 50. In cases of inadequate analgesia, patients were given additional doses of fentanyl 1 μg kg^{-1}.

Bradycardia was defined as HR<40 beat min^{-1} and hypotension as a decrease in SAP>20% of the baseline value. Hypotension was treated by infusion of lactated Ringer's solution 3–5 ml kg^{-1}, and if necessary, with ephedrine 5 mg i.v. Bradycardia was treated with atropine 0.5 mg i.v. The frequency of hypotension, bradycardia, inadequate analgesia, and supplemental fentanyl doses was recorded.

To assess intraoperative awareness, a number was repetitively recited to each patient four times during anaesthesia at 5, 10, 15, and 20 min. In the postoperative period, the patients were specifically questioned for recall of this number.

Table 1 Patient characteristics of the groups. Values are numbers or mean (SD)

	Group T (n=18)	Group L (n=18)	Group C (n=18)
Age	49 (8)	50 (8)	48 (9)
Gender	7 women; 11 men	8 women; 10 men	9 women; 9 men
Height (cm)	165 (30)	161 (33)	162 (35)
Weight (kg)	71 (7)	68 (11)	74 (12)
Anaesthesia time (min)	176 (31)	181 (32)	186 (29)

At the end of the operation, with the end of the skin closure, propofol infusion was stopped. The time to reach a BIS level of 80 (BIS80) and the time to extubation (BIS≥90 *and* fulfilled clinical criteria for extubation) (Extt: extubation time) were also recorded. After the end of the study period, the epidural infusion in Group C was changed to an analgesic one by an independent anaesthetist to manage the postoperative analgesia.

Statistical analysis

Statistical analysis was performed with GraphPad InStat version 3.00 for Windows 95 (GraphPad Software, San Diego, CA, USA, www.graphpad.com). Analysis of variance (ANOVA) was used to evaluate the differences in patient characteristics, BIS values, ID and MD of propofol, and BIS80 and Extt between the groups. *Post hoc* comparisons were made using Tukey test. Epidurally administered volumes to achieve a block at Th-4 in Groups T and L were compared with Student's *t*-test. To compare the frequency of hypotension, bradycardia, and inadequate analgesia, an appropriate χ^2 test was used. The results are presented as mean ± SD, and $P<0.05$ was regarded as statistically significant.

Results

There were no statistically significant differences with respect to patient characteristics and the anaesthesia time between the groups (Table 1). The patients operated had all been diagnosed with kidney tumour. None of the patients has had an intraoperative awareness regarding the postoperative testing. There were no significant differences between BIS values in the three groups. There were also no significant differences between the values of HR and systolic arterial pressures in different measurement times in three groups (Table 2).

The mean volume to obtain a block at Th4 (1) was significantly lower in Group T than in Group L [10.7 (1.5) ml *vs* 14.7 (1.0) ml; $P<0.001$]. After application of these volumes, in all patients in Groups T and L, a block level between Th3 and Th5 could be obtained; and no patient had to be excluded because of a too high (>Th3) or too low (<Th5) block.

Table 2 Haemodynamic data during the first 120 min and before the extubation: HR (beats min^{-1}); and the MAP (mm Hg) values. T, thoracic epidural+general anaesthesia; L, lumbar anaesthesia+general anaesthesia; C, general anaesthesia. There were no differences between the groups in any measurement. Values are mean (SD)

Groups	HR (min^{-1})			MAP (mm Hg)		
	T	L	C	T	L	C
Preinduction	76 (10)	71 (12)	73 (11)	94 (12)	97 (13)	98 (13)
Postinduction	66 (11)	61 (12)	67 (13)	79 (11)	77 (10)	76 (12)
Postintubation	79 (17)	70 (19)	70 (15)	87 (11)	89 (11)	85 (13)
15 min	79 (16)	71 (16)	79 (16)	91 (12)	91 (12)	89 (14)
30 min	75 (16)	74 (15)	73 (14)	90 (10)	91 (13)	93 (13)
60 min	73 (19)	77 (17)	74 (16)	92 (13)	93 (13)	90 (14)
90 min	71 (20)	72 (15)	76 (18)	88 (12)	87 (12)	90 (13)
120 min	71 (18)	72 (15)	74 (17)	90 (11)	89 (14)	89 (12)
Preextubation	81 (21)	82 (18)	83 (20)	98 (18)	99 (16)	99 (16)

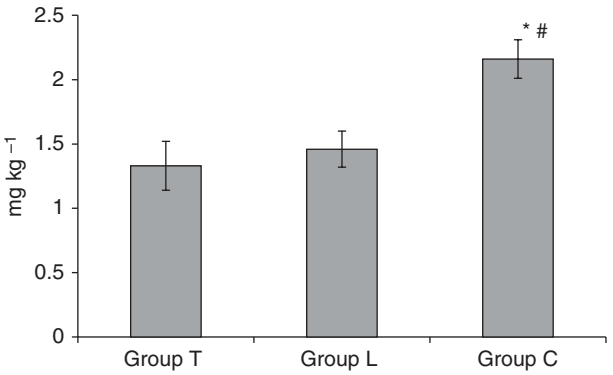

Fig 1 Propofol doses for induction (ID) (mean and SD) ($P<0.0001$). *$P<0.001$ for Group C (control) *vs* Group T (thoracic); #$P<0.001$ for Group C *vs* Group L (lumbar). Note that Groups T and L received *different* amounts of local anaesthetics+opioid via the epidural route (T: via Th7–8; L: via L3–4) to obtain the same dermatomal level of Th4 [Group T: 10.7 (1.5) ml *vs* Group L: 14.7 (1.0) ml; $P<0.001$].

The propofol doses required for induction of anaesthesia (ID) were significantly higher in the control group compared with that in Groups T and L (Fig. 1) [for Groups C, T, and L: 2.16 (0.15) *vs* 1.33 (0.19) *vs* 1.46 (0.14) mg kg^{-1}, respectively, $P<0.0001$; for Group C *vs* Group T and Group C *vs* Group L: $P<0001$]. There was no significant difference between Groups T and L regarding this parameter.

In propofol doses required for the maintenance (MD), there were significant differences between all groups [3.82 (0.9) *vs* 5.8 (1.32) *vs* 9.21 (0.55) mg kg^{-1} h^{-1} in Groups T, L, and C, respectively, $P<0.0001$; for all *post hoc* comparisons, $P<0.001$] (Fig. 2).

The time to reach BIS80 and Extt were also statistically different between all groups ($P<0.0001$; all *post hoc* comparisons for both parameters: $P<0.001$) (Table 3).

There has been no change in BIS level between performance of the epidural anaesthesia and induction.

After the induction, bradycardia was observed in three, three and one patients in Groups T, L, and C, respectively

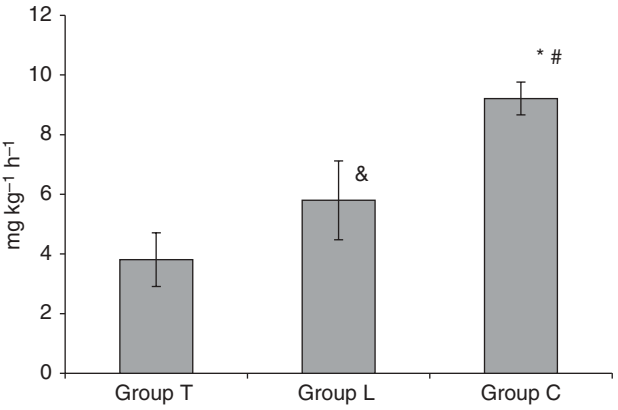

Fig 2 Propofol doses for maintenance (MD) (mean and SD) ($P<0.0001$). *$P<0.001$ for Group C *vs* Group T; #$P<0.001$ for Group C *vs* Group L; &$P<0.001$ for Group L *vs* Group T. Note that Groups T and L received the *same* amounts of local anaesthetics+opioid via the epidural route with no regard to keeping the same dermatomal level.

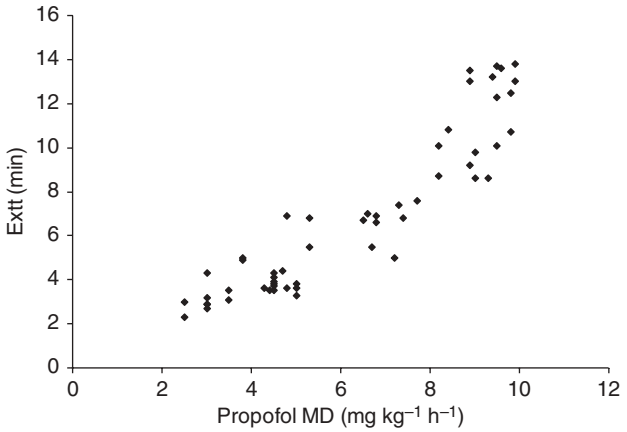

Fig 3 Correlation between the maintenance doses (MD) of propofol and the extubation time (Extt). Regardless of which group the patients came from, there is a significant relationship ($r^2=0.85$, $P<0.0001$).

Table 3 BIS80 (time to reach a BIS level of 80 after cessation of propofol infusion) and Extt (time from after cessation of propofol infusion to the extubation) in the groups. Values are mean (SD). For both parameters, *post hoc* comparisons are also significantly different ($P<0.001$) in all groups

	Group T	Group L	Group C	ANOVA (*P*-value)
BIS80 (min)	1.40 (0.52)	3.30 (1.16)	8.10 (0.99)	<0.0001
Extt (min)	3.4 (0.52)	5.8 (1.32)	11.4 (1.96)	<0.0001

($P>0.05$), and hypotension was seen in four, three, and one patients in Groups T, L, and C, respectively ($P>0.05$).

In Group C, additional doses of fentanyl 1 μg kg^{-1} i.v. was necessary, 3.5 (1.3) [min. 1, max. 6] times in all patients during the operation. On the other hand, in Groups T and L only one patient in each group needed one additional dose fentanyl ($P<0.001$ for Group C *vs* Group T and Group C *vs* Group L).

A correlation between the MD of propofol and Extt was investigated. There was a significant correlation in each group (in Group T: $r^2=0.38$, $P=0.00\,627$; in Group L: $r^2=0.47$, $P=0.002$, and in Group C: $r^2=0.27$, $P=0.02\,813$) and overall in all 54 patients ($r^2=0.85$, $P<0.0001$) (Fig. 3, Table 3).

Discussion

This study has shown that similar sensorial levels of epidural anaesthesia have decreased the requirement in propofol for the induction in similar amounts, although they have been applied at different levels with higher doses of local anaesthetics in Group L. Moreover, similar amounts of the local anaesthetics during maintenance have resulted in different MDs of general anaesthetics, depending on their application level. Both results confirm our hypothesis that the anaesthetic concentration rather than the dose of the applied local anaesthetic of the epidural anaesthesia plays a role in the hypnotic effects of the epidural anaesthesia.

Many studies have shown that local anaesthetics administered via different routes cause a decrease in the requirement of general anaesthetic drugs. Hodgson and colleagues have demonstrated the general anaesthetic effects of the epidural anaesthesia first in a clinical setting[1] and afterwards with BIS.[3]

Three mechanisms are suggested for the reduction of the requirement of the general anaesthetic agents when combined with epidural anaesthesia: (i) deafferentation: decreased stimulation of reticular activating system followed by the interruption of the spinal afferent inputs; (ii) systemic general anaesthetic effects of absorbed local anaesthetic; and (iii) subanaesthetic concentrations of epidural local anaesthetic depressing spinal cord motor function.

Although there are controversial results concerning all of these mechanisms in several studies, the most speculated one is the deafferentation. Our results in this study also support this first possible explanation. This was supported by a number of other studies including the ones of Hodgson and colleagues.[1 3] However, according to other studies, it appears that the second and third possible mechanisms do play some role in the interaction of local and general anaesthetics.[6 7 11] In a previous study, we have shown that i.m. administration of local anaesthetics lead to a reduction in both the IDs and MDs of propofol to achieve the same BIS value.[8] Therefore, it can be assumed that the other mechanisms play a role in the decrease in general anaesthetic doses, whereas 'increased deafferentation', regarding our current study, can be considered as the major mechanism.

Regarding the 'deafferentation', blunting the peripheric stimuli via a neuroaxial block and the consequent sympathetic block affects also the level of consciousness, leading to a decrease in the dose of the agent to achieve the same level of hypnosis/sedation.[1–4]

It has been shown that some other drugs (e.g., beta-blockers) can also have a similar hypnotic sparing effect.[12] Similarly, remifentanil can also interact synergistically with propofol during surgery, whereas its contribution in the absence of stimulation (as it was also in our study) seems limited.[13]

In another study, we have reported that in spinal anaesthesia, high levels of spinal block (with higher doses of local anaesthetics) were associated with a lower dose of propofol as sedative.[5] However, in the setting of that study, it was not possible to conclude whether the level of the spinal block or the dose of the local anaesthetic has led to this result. Recently, in a study with a similar protocol with the epidural anaesthesia, it was demonstrated that the higher concentration (1% *vs* 0.2%) of ropivacaine was associated with a more exaggerated decrease in sevoflurane to keep the same BIS level.[14] However, again, it cannot be concluded from this study whether the level of block (Th8 *vs* Th5) or the dose (same volumes of different concentration) of the administered ropivacaine has led to this difference. The opportunity of the epidural anaesthesia to apply in different levels in the present study has allowed it to differentiate between the level of the block and the dose of the local anaesthetic. After loading, similar sensorial levels of epidural anaesthesia have been achieved in Groups T and L, which has led to a similar effect on general anaesthesia. For the maintenance, in contrast, equal volumes have been administered through different levels to obtain a higher level of epidural block in Group T compared with Group L during the operation, which has resulted in a further decrease in general anaesthetic requirement.

Another important discussion in this topic is whether local anaesthetics *per se* have a general anaesthetic effect or act as an additive to general anaesthetics. In the studies of Ishiyama and colleagues[15] and Pollock and colleagues,[11] it has been reported that even before the general anaesthesia or systemic sedation, local anaesthetics show a hypnotic effect via the epidural and spinal route, respectively. On the other hand, in other studies including the present one and the ones performed in our clinics, local anaesthetics show a hypnotic effect (reflected in BIS) only after the initiation of general anaesthesia/systemic sedation. This controversy can be explained by certain differences in the protocols of the studies (e.g. healthy volunteers *vs* preoperative anxiety of patients). In the present study, there are two results confirming that epidurally administered local anaesthetics have only additive effects to general anaesthesia without a sole hypnotic effect. First, there was no decrease in the BIS level after the epidural and before the general anaesthesia. Additionally and more importantly, the recovery times (BIS80 and Extt) were associated with the propofol doses, but not with the bupivacaine doses. Although the total applied bupivacaine dose was higher in Group L compared with Group T, the recovery times (BIS80 and Extt) were significantly shorter in Group T, probably as a result of lower propofol doses.

Both Groups L and T were associated with a significant decrease in propofol doses required for both induction and maintenance when compared with Group C. This is not only a well-known fact of daily practice anymore; it is also a well-studied theory since the studies of Hodgson.[1 3] However, not only is the mechanism of this interaction rebuttable from the theoretic point of view, more importantly, the degree of the reduction of the doses of general anaesthetics is also a less-known topic from the practical point of view. It appears that multiple factors including the application route, dose, and distance to central nervous system (for the epidural route) affect the degree of reduction. In this study, routine doses of bupivacaine in a commonly used combination of local anaesthetic+opioid were used for lumbar and thoracic epidural anaesthesia. With these doses, thoracic epidural anaesthesia has led to a 38% decrease in induction and to a 58% decrease in MDs of propofol compared with pure general anaesthesia, while these values were 32 and 39.5%, respectively, with lumbar epidural anaesthesia.

An important limitation of the study can be the difference in fentanyl requirements. Because of the interaction of opioids (fentanyl in our study) and hypnotics (propofol in our study), different amounts of fentanyl can presumably have an effect on the propofol requirements. In a previous study, it has been shown that there is a synergistic interaction of remifentanil and propofol during surgery; but in the absence of stimulation (similar to our study), this blunting effect is limited.[13] In our study, the indications of fentanyl and propofol were defined distinctly in the study protocol and this protocol was kept during the entire period of the operations. Propofol was administered only to keep BIS between 40 and 50; and fentanyl was administered only in hypertension or tachycardia, if the BIS was between 40 and 50. Although the patients in Group C have needed significantly higher amounts of fentanyl compared with both epidural groups, the necessary dose of propofol for maintenance was still higher in these patients. This can be explained again by the additive effects of epidural anaesthesia. Moreover, supplemental doses of fentanyl could also contribute to the delay in recovery from anaesthesia. From ethical reasons, systemic analgesia has been necessarily applied to the patients in the control group by the blinded anaesthetist in contrast to both epidural groups. It is considered that systemic opioids do not affect the BIS measurements; however, there are also some controversies in this topic. In this study, we have preferred fentanyl boli instead of any infusion of an opioid to observe any changes in the BIS level after fentanyl application. No particular change in the BIS level was observed after the administration of fentanyl in any patient.

Haemodynamic changes can cause some changes in cerebral blood flow with consequent effects on BIS. However, there were no significant differences in the frequencies of haemodynamic instabilities between the groups. Although it could be expected that the thoracic

anaesthesia could lead to hypotension, bradycardia, or both during the combination with general anaesthesia, this has not been the case, probably because of the fine titration of propofol infusion rate according to BIS, which was significantly lower during both induction and maintenance compared with control group. Moreover, according to the protocol, hypotension is prevented and treated strictly with fluids and ephedrine, so that a BIS change as a result of hypotension does not seem possible.

Another limitation can be that it was not possible to determine the level of the sensorial block during the application of the MDs of the epidural medication. However, the block level after the first doses was fixed to be Th4 (1); and it can be assumed that after this initial similar block, application of the same volumes via thoracic epidural route would lead to a higher sensorial block compared with the application via the lumbar epidural route.

In some similar studies, a 'target-controlled infusion' (TCI) system has been used.[16] However, there are also studies showing that TCI and 'manual-controlled infusion' have resulted in similar depth of anaesthesia and haemodynamic stability.[17] We have not used a TCI system to adjust the propofol concentration. However, there was a relative homogeneous distribution of patients regarding age, gender, weight, and height (Table 1), and therefore, it can be assumed that the propofol predicted concentrations in different stages of the operation would not differ relevantly.

Interestingly, local anaesthetics do not only interact with the hypnotic component of anaesthesia, it has been shown that they are also potent analgesics when administered i.v.[18]

It can be concluded that the epidural anaesthesia potentiates the effects of general anaesthesia. This potentiating effect is associated more with the anaesthetic level than the administered dose. A thoracic epidural anaesthesia with commonly used doses has led to a 38% in ID and 58% in MD and a lumbar epidural anaesthesia to a 32% in ID and 39.5% in MD decrease in propofol requirement compared with general anaesthesia only.

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