Additional phenytoin is frequently needed in patients undergoing craniotomy for supratentorial tumour

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Phenytoin is generally prescribed to patients with supratentorial tumours to decrease the risk of seizures. Earlier studies showed that plasma phenytoin concentration may not be in the therapeutic range despite continued therapy [1]. During craniotomy for a supratentorial tumour, an intraoperative loading dose of phenytoin is generally used to prevent postoperative seizures [2,3]. In our institution, it has been common practice not to administer phenytoin intraoperatively. To understand the consequences of our practice of withholding intraoperative phenytoin, we measured perioperative serum phenytoin concentration in a group of patients undergoing supratentorial tumour surgery. We also tried to determine the factors influencing postoperative serum phenytoin concentrations.

Twenty-five adult patients (ASA I or II) of either sex, receiving phenytoin for a period not less than 7 days before supratentorial surgery, were studied after institutional approval and informed consent. On the day of surgery, 300 mg of phenytoin was administered either orally or intravenously 4 h before surgery. The anaesthetic technique comprised of induction with thiopentone (5–6 mg kg^{-1}), tracheal intubation facilitated by a muscle relaxant and maintenance with either isoflurane or propofol. Intraoperative analgesia was provided by fentanyl. Serum phenytoin concentration was measured before induction, immediately after surgery and 24 h after surgery. The assay, performed by a chemiluminescence technique using an Immulite Assay Kit® (DPC®; Los Angeles, CA, USA), permitted the measurement of total phenytoin concentration. The following parameters were recorded in all patients: duration of anaesthesia and surgery, volume of crystalloids, colloids and blood products administered, volume of urine output and blood loss, and occurrence of immediate postoperative seizures.

A repeated-measures analysis of variance (ANOVA) with Bonferroni's test was used to find out significant differences among the preinduction, immediate postoperative and delayed postoperative serum phenytoin concentrations. Study variables in patients with therapeutic and subtherapeutic concentrations of phenytoin were compared by one-way ANOVA for continuous data and a χ^2-test for categorical variables. Pearson's test was used to correlate preinduction phenytoin concentration and its decrease in the immediate postoperative period. Logistic regression analysis was used to determine the independent predictors of immediate postoperative subtherapeutic serum phenytoin concentration. A P value of <0.05 was considered significant.

There were 17 male and 8 female patients in the study. Their age was 38 ± 12 yr and body weight was 56 ± 11 kg. Twelve patients had a preoperative history of seizures. The preinduction serum phenytoin concentration was highly variable among the patients (range 2.5–37.3 $\mu g\,mL^{-1}$ (95% CI = 9.8–17.8 $\mu g\,mL^{-1}$)). Despite continuous medication until the morning of surgery, 11 patients (44%) had a subtherapeutic concentration of serum phenytoin (normal range 10–20 $\mu g\,mL^{-1}$) in the preinduction sample. Serum phenytoin concentration was significantly lower in the immediate postoperative sample compared with the preinduction sample (9.5 ± 7.0 vs. $13.8 \pm 9.4\ \mu g\,mL^{-1}$; $P < 0.001$). The concentration increased significantly in the delayed postoperative sample ($11.8 \pm 8.0\ \mu g\,mL^{-1}$; $P < 0.001$). The decrease in phenytoin concentration in the immediate postoperative sample correlated with its preinduction value ($P < 0.01$; $r = 0.8$). Seizures within 24 h of surgery occurred in two patients. Only one of these patients had a preoperative history of seizures. Serum phenytoin concentration was within the therapeutic range (16.3 and 10.4 $\mu g\,mL^{-1}$) in both the patients.

In the immediate postoperative period, serum phenytoin concentration was in a subtherapeutic range in 15 out of the 25 study patients. On univariate analysis, the variables that were significantly different between the therapeutic and subtherapeutic groups were the patient's gender, preinduction phenytoin concentration, blood loss, blood transfusion, duration of surgery and duration of anaesthesia (Table 1). Of these, preoperative phenytoin level, intraoperative blood transfusion and the duration of surgery/anaesthesia were found to be the independent predictors of low serum phenytoin concentration in the immediate postoperative period ($P < 0.05$).

The value of prophylactic administration of antiepileptic drugs in patients with brain tumours remains controversial. Some authors claim a significant decrease in the incidence of seizures in the

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Table 1. Study variables in patients with subtherapeutic and therapeutic postoperative phenytoin concentration.

Variable	Subtherapeutic group	Therapeutic group	*P* value
Age (yr)	37 ± 12	39 ± 11	0.737
Gender (M : F)	8 : 7	9 : 1	0.045
Weight (kg)	57 ± 13	54 ± 6	0.466
Crystalloids (mL)	2830 ± 1034	2660 ± 996	0.687
Blood loss (mL)	905 ± 853	345 ± 185	0.05
Urine output (mL)	1400 ± 762	1560 ± 834	0.625
Preinduction Serum Phenytoin ($\mu g\,mL^{-1}$)	8.1 ± 4.7	22.5 ± 7.5	0.000
Duration of anaesthesia (min)	345 ± 99	256 ± 55	0.018
Duration of surgery (min)	278.7 ± 82.6	202 ± 59.6	0.019
Blood transfusion	8/15	0/10	0.004
Need for colloids	5/15	2/10	0.488

Data are mean ± SD or number of patients.

postoperative period [2,3] with preoperative antiepileptic therapy. However, in one study, phenytoin doses aimed at maintaining serum phenytoin concentrations in the 10–20 $\mu g\,mL^{-1}$ range did not decrease the incidence of postoperative seizures [4]. One meta-analysis showed a statistically insignificant reduction of postoperative convulsions with prophylactic anticonvulsant and suggested the need for further investigation of the issue [5].

In our study, preoperative serum phenytoin concentration was highly variable with 44% of the patients having subtherapeutic concentrations as has been reported earlier [1]. Widely variable clearance, as is known to occur even in normal individuals, could probably be the reason for this variation. Another possible cause is the interaction between dexamethasone and phenytoin as has been reported earlier [6]; all our patients had been receiving dexamethasone for several days before surgery. There was a linear correlation between preoperative serum phenytoin concentration and its decrease in the intraoperative period, which is possibly related to the first-order kinetics of phenytoin.

We found that preinduction serum phenytoin concentration, need for blood transfusion and the duration of surgery/anaesthesia were independent predictors of low phenytoin concentration in the immediate postoperative period. A simple process of dilution caused by blood and fluid replacement might be responsible for the decrease in phenytoin concentration. Long-duration surgery might have caused increased excretion and lower serum concentration. In a recent study by Yeh and colleagues [1], less than 50% of the patients had a therapeutic level of serum phenytoin and the predictors of low serum phenytoin concentration were the same as in our study.

Despite withholding the intraoperative phenytoin dose, only two patients had postoperative seizures within 24 h. The small sample size in the study prevents drawing serious conclusions regarding the incidence of perioperative seizures with and without intraoperative loading. Given the subtherapeutic phenytoin concentration in a major proportion of our patients, it is advisable to administer an intraoperative dose of phenytoin to achieve the therapeutic level. Whether these additional doses cause toxic levels of phenytoin in patients in whom the metabolic pathways are already saturated also remains to be seen. A more rational approach would be to decide the dosing based on serum phenytoin levels measured preoperatively. It would also be interesting to study the influence of perioperative corticosteroids on serum phenytoin levels.

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Laparoscopic donor nephrectomy – postoperative pain treatment

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Since the first reports of laparoscopic donor nephrectomy (LDN) two decades ago, it has become a routine surgical procedure. Most publications favour the laparoscopic procedure in terms of better pain control, faster recovery, less fatigue and better quality of life of the donor compared with mini-incision open donor nephrectomy (ODN). However, both procedures have equal safety and graft function.

When LDN was introduced in our hospital 3 yr ago, a literature search confirmed that LDN was less painful than ODN (i.e. postoperative morphine consumption decreased from 123.6 ± 88.0 mg for ODN to 24.4 ± 14.8 mg for LDN) [1]. Consequently, we abandoned epidural analgesia for all donor nephrectomies and used a standard multimodal approach for postoperative pain treatment: morphine patient-controlled analgesia (PCA) as a first-line analgesic, combined with paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) as second-line analgesics.

Two years later, we undertook a retrospective review involving 58 donors: 19 intraperitoneal laparoscopic, 38 open and one laparoscopic converted into open. This review has demonstrated that morphine requirements in both groups were similar. The median dose of administered PCA morphine was 68 mg in the LDN group and 69 mg in the mini-incision ODN group. The difference was not significant (t-test, $P > 0.05$). the overall duration of use of morphine PCA was 42 h, and it was similar for both the groups (LDN vs. ODN, 47 vs. 40.5 h). The pain level was measured with a standard categorical scale (0–4), and the highest level of pain score at each day was recorded for the study. Of the patients, 38% had the highest score 1, 37.9% had score 2 and 27.6% had score 3. There were no significant differences in the pain scores between patients who underwent LDN and ODN (χ^2-test, $P > 0.05$). Although NSAIDs had been prescribed to all patients, they were used in only 40% of patients, and paracetamol was used regularly. Our results were different from a recently published randomized controlled study from The Netherlands, where it was found that the morphine requirements of the patients in LDN group were less compared with the mini-incision ODN group [2]. The median morphine requirements in the LDN group were 16 mg (0–93) compared with 25 mg (1–107) in the ODN group, which was highly significant [2]. Other studies also reported less or no opioid requirement following LDN. A study from the USA showed that 290 LDN had good pain control with oral medication when they used preoperative bowel rest and ketorolac as a bolus every 6 h [3]. Their patients were discharged from hospital 24 h after surgery [3]. Another retrospective analysis from Switzerland on 203 live kidney donors has shown that 87% retroperitoneoscopic donor nephrectomies had subcutaneous analgesia, only 11.7% had morphine PCA and 1.3% (one patient) had epidural analgesia. For ODN, 55.7% had an epidural, only 29.1% had PCA and even 15.2% had subcutaneous analgesia [4].

Finally, a randomized controlled study from Norway had 63 LDN and 59 ODN. With the addition of pro-paracetamol 2 g four times and ketorolac 30 mg three times on the day of surgery and on the first 2 postoperative days, their patients' morphine consumption was 43.5 mg for LDN and 52.1 mg for ODN. Postoperative morphine consumption in this study was higher than in other studies, but still approximately 20 mg less than that in our study. There were differences between LDN and ODN, and pain scores were low: Pain score at rest was 1.0 for LDN and 1.1 for ODN [5].

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