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ORIGINAL PAPER

Plasma Concentrations of Brain-derived Neurotrophic Factor in Patients Undergoing Minor Surgery: A Randomized Controlled Trial

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Abstract We measured perioperative plasma concentrations of brain-derived neurotrophic factor (BDNF), a major mediator of synaptic plasticity in the central nervous system, in males, 30–65 years old, undergoing lumbar or cervical discotomy. Patients were randomly allocated to a general anesthetic with propofol induction and maintenance or with thiopental induction and isoflurane maintenance. BDNF plasma concentrations were measured before induction (baseline), 15 min after induction but before start of surgery, at skin closure, in the post-anesthetic care unit, and 24 h postoperatively. Data from 26 patients (13 in each group) were analyzed. At each time point, BDNF plasma concentrations showed large variability. At baseline, concentrations were 631 ± 337 (mean ± SD) pg ml^{-1} in the propofol group and were 549 ± 512 pg ml^{-1} in the thiopental–isoflurane group ($P = 0.31$). At 15 min, concentrations significantly decreased in the propofol group (247 ± 219 pg ml^{-1}, $P = 0.0012$ compared with baseline) but remained unchanged in the thiopental–isoflurane group (597 ± 471 pg ml^{-1}, $P = 0.798$ compared with baseline). At skin closure and in the post-anesthetic care unit, concentrations were not different from baseline in both groups. At 24 h, concentrations significantly decreased below baseline in both groups (propofol: 232 ± 129 pg ml^{-1}, $P = 0.0015$; thiopental–isoflurane: 253 ± 250 pg ml^{-1}, $P = 0.016$). In the propofol group, there was a weak but statistically significant positive correlation ($R^2 = 0.38$, $P = 0.026$) between the duration of surgery and BDNF plasma concentrations at skin closure. These data suggest that in males undergoing elective minor surgery, BDNF plasma concentrations show a specific pattern that is influenced by the anesthetic technique and, possibly, by the duration of surgery.

Keywords Anesthesia · BDNF · Isoflurane · Plasma · Propofol

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Introduction

Brain-derived neurotrophic factor (BDNF), a non-glycosylated secretory polypeptide, is a member of the neurotrophin family of growth factors. It plays a fundamental role in the survival and differentiation of numerous neuronal subpopulations during development [1], and is required for the maintenance of neuronal viability in adulthood [2]. BDNF is a major mediator of short- and long-term neuronal plasticity in the adult central nervous system (CNS) [3]. Synthesis, secretion and actions of BDNF are largely mediated by neuronal network activity and, in turn, activity-dependent secretion of BDNF can induce both rapid and long-term changes in synaptic efficacy [3]. In rodents, BDNF has been shown to mediate higher-order activities, such as learning, memory, and

behavior [4], and also exerts a neuroprotective role in either global [5] or focal [6] brain ischemia.

BDNF is detectable in the human blood where serum concentrations of this protein are more than 100-fold higher than plasma levels [7, 8]. This difference is due to the large amount of BDNF stored in platelets that degranulate during the clotting process [9, 10]. The contribution of the multiple potential cellular sources of BDNF found in the human plasma remains to be defined. In fact, in addition to the CNS, BDNF is also synthesized and secreted by peripheral organs, such as vascular endothelia and visceral epithelia [11, 12]. Importantly, BDNF crosses the blood-brain barrier by a high-capacity, saturable transport system [13], and, in rodents, a positive correlation has been reported between serum and cerebral cortex BDNF levels [14]. In line with these results, physical activity, known to increase BDNF levels in the rodent brain [15, 16], was also shown to increase BDNF blood concentrations in humans, and this was accompanied by an improvement in cognitive function [17]. On the other hand, decreased plasma and serum BDNF levels were reported in patients with major depressive disorders [18–20], a pathology associated with impaired BDNF signaling in the CNS [21].

Anesthetics are known to cause profound depression of neuronal activity and the important role of activity-dependent rapid release of BDNF from its intracellular stores in order to promote appropriate neuronal network function is now well established [22, 23]. Recent results indicate that anesthesia might modulate BDNF levels in the rodent brain [24]. Theoretically, based on the positive correlation between brain and blood levels of BDNF, serial measurements of BDNF blood concentrations may inform about the temporal evolution pattern of this protein in the CNS during the perioperative period. This may allow comparing the influence of different anesthesia protocols as well as to evaluate the impact of the perioperative stress response on BDNF kinetics. Information obtained from such studies would provide further hints on the complex role of anesthetics on neural network function and might enable to determine whether this neurotrophic factor could be used as a surrogate to monitor brain function in surgical patients. To answer these questions, we need to know first if, and to what extent, anesthesia and/or surgery are influencing the temporal evolution pattern of BDNF blood concentrations in the perioperative period.

Hence, the goal of the present study was to evaluate perioperative BNDF plasma concentrations in a well-controlled surgical setting. Since BDNF plasma levels have been shown to be dependent on gender, age and body weight [7], we focused on males, 30–65 years of age, and with a body mass index of 20–30. We also investigated whether two frequently used general anesthesia techniques, i.e. a total intravenous anesthesia using propofol versus a general anesthetic using thiopental for induction and isoflurane for maintenance, modify differently intra- and postoperative BDNF kinetics.

Materials and Methods

Inclusion and Non-inclusion Criteria

This study was approved by the ethics committee of University Hospitals of Geneva and was conducted from November 2005 to December 2006. Prior to enrollment, participating subjects gave written informed consent. All patients underwent elective lumbar or cervical discal hernia repair, scheduled to last 1–3 h. We considered these procedures as minor surgery, without significant hemorrhagic risk, and minimal perioperative stress response. Patients with underlying organ and known psychiatric illnesses as well as those taking steroids and anti-depressants were not considered.

Anesthesia

Patients received 7.5 mg midazolam orally 30 min prior to anesthesia. Standard monitoring included three-lead ECG, non-invasive blood pressure, end-tidal CO_2, and peripheral capillary oxygen saturation. Electrodes for Bispectral Index (BIS), standardized EEG monitoring which estimate the depth of anesthesia, were placed on the forehead as recommended by the manufacturer. BIS values between 40 and 60 are considered as adequate depth of anesthesia.

Upon arrival in the operating room, an 18G catheter was placed intravenously on the back of a hand and 10 ml of blood were drawn for baseline measurements of BDNF plasma concentrations. Anesthesia was then induced using the same peripheral catheter. Once the patient was anesthetized, a second intravenous catheter was placed on the back of the contra-lateral hand and was subsequently used for fluid and anesthesia management. All blood samples were drawn through the first catheter.

Patients were randomly allocated using opaque envelops to one of two groups. In the propofol group, anesthesia was induced and maintained with propofol using a target control infusion system (Base Primea, Fresenius-Vial, Brezins, France) and the pharmacokinetic model of Schnider et al. [25]. In the thiopental–isoflurane group, anesthesia was induced using 5 mg kg^{-1} thiopental followed by isoflurane. All patients received sufentanil 0.3 μg kg^{-1} intravenously before endotracheal intubation followed by an intravenous infusion of 0.2 μg kg^{-1} h^{-1} throughout surgery. Endotracheal intubation was facilitated using a

single dose of rocuronium 0.6 mg kg^{-1}. Patients were normo-ventilated with an oxygen-air mixture (FiO_2 40%). Bispectral Index was maintained between 40 and 60 throughout surgery using incremental concentrations of propofol or isoflurane.

In the recovery room and on the ward, patients received acetaminophen, non-steroidal anti-inflammatory drugs and morphine on request to treat postoperative pain.

Measurements

Five venous blood samples (10 ml each) were obtained from each patient during the study period, i.e. (i) before induction (baseline), (ii) 15 min following induction, but before start of surgery, (iii) at skin closure, (iv) in the post-anesthetic care unit (2 h after the end of surgery), and (v) 24 h postoperatively. Blood samples were drawn into heparinized containers and put immediately on ice until processing. Plasma was obtained by centrifugation of the heparinized containers for 15 min at 2,000*g* at 4°C. Supernatants were aliquoted and stored at −80°C until measured. BDNF plasma concentrations, using non-diluted plasma samples, were measured using commercial enzyme-linked immunosorbent assays (ELISA) according to the manufacturer's instructions (Quantikine® Human BDNF Immunoassay, R&D Systems, Minneapolis, USA). Using this assay, the minimum detectable dose of BDNF is typically less than 20 pg ml^{-1}.

Statistical Analysis

To compare BDNF values among the two anesthesia techniques, we used the non-parametric Mann–Whitney *U*-test. For comparison of BDNF values within each group, the two-way ANOVA on log-transformed BDNF values followed by the Bonferroni test was applied. Correlations were estimated using the Spearman's correlation coefficient. A P-value < 0.05 was regarded as statistically significant. Logistic regression was used to test for potential relationships between different factors (for instance, duration of surgery) and BDNF plasma concentrations. All data were analyzed using GraphPad Prism software (GraphPad Software Inc., San Diego, CA, USA).

Results

Thirty patients, 15 in each group, were randomized. Due to technical problems during blood processing, data from 4 patients (2 from each group) had to be excluded. Characteristics of the remaining 26 patients were comparable between the two groups (Table 1). As these procedures can all be classified as minimal invasive surgery, there were no relevant blood losses in any patient.

Table 1 Demographic and clinical characteristics of patients

	Anesthesia procedure		*P*-value
	Propofol	Thiopental/isoflurane	
n	13	13	
Age (years)	48.8 ± 9.5	48.2 ± 7.7	0.98
Weight (kg)	85.2 ± 10.1	79.5 ± 7.7	0.15
Height (cm)	176.5 ± 7.8	176.3 ± 8.3	0.8
BMI	27.1 ± 3.5	25.6 ± 2.1	0.13
Duration of surgery (min)	98 ± 32	88 ± 54	0.23
Pathology			
Lumbar discus hernia	10	9	
Cervival discus hernia	3	4	

At baseline, BDNF plasma concentrations were 631 ± 337 (mean ± SD) pg ml^{-1} in the propofol group and were 549 ± 512 pg ml^{-1} in the thiopental–isoflurane group ($P = 0.31$) (Fig. 1; Tables 2 and 3). At 15 min, BDNF plasma concentrations were significantly decreased in the propofol group (247 ± 219 pg ml^{-1}, $P = 0.0012$ compared with baseline) but remained unchanged in the thiopental–isoflurane group (597 ± 471 pg ml^{-1}, $P = 0.798$ compared with baseline) (Figs. 1 and 2). At this time point, the difference in BDNF values between groups was statistically significant ($P = 0.0012$).

At skin closure and in the post-anesthetic care unit, BDNF plasma concentrations were not different from baseline in both groups, and there were no differences between groups (Fig. 1; Tables 2 and 3). At this time point, the variability in BDNF plasma concentrations was maximal; in the propofol group, values ranged from 84 to almost 12,000 pg ml^{-1}; in the thiopental–isoflurane group, they ranged from 22 to more than 2,500 pg ml^{-1}.

At 24 h, BDNF plasma concentrations decreased below baseline in both groups (Fig. 1; Tables 2 and 3). In the two groups, the difference between baseline and the 24 h value reached statistical significance (propofol: $P = 0.0015$; thiopental–isoflurane: $P = 0.016$).

Since wide variations in BDNF plasma concentrations were observed at each time point, we evaluated potential sources of this variability. We tested correlations between BDNF values and patient characteristics (age, weight, height, body mass index). This was done with BDNF values at each time point and for both anesthesia groups separately. There was no evidence of any correlation between BDNF plasma concentrations and the tested parameters at any time point.

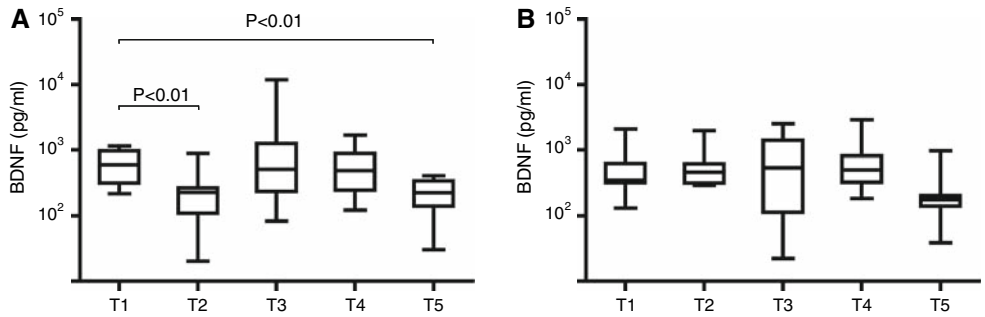

Fig. 1 Changes in BDNF plasma concentrations during the perioperative period in patients who where randomized to one of two groups (13 patients each): propofol induction and maintenance (**a**) or to thiopental induction and isoflurane maintenance (**b**). T1 = before induction (baseline); T2 = 15 min following induction but before initiation of surgery; T3 = skin closure; T4 = post-anesthetic care unit (2 h after the end of surgery); T5 = 24 h postoperatively. The top, bottom and line through the middle of the boxplots correspond to the 75th percentile (top quartile), 25th percentile (bottom quartile), and 50th percentile (median) respectively. The whiskers on the bottom extend from the 10th percentile and on the top from the 90th percentile

Table 2 Temporal evolution pattern of BDNF plasma levels during the perioperative period in patients receiving propofol anesthesia

Propofol ($n = 13$)	T1	T2	T3	T4	T5
Mean	631	247	1747	645	233
Median	610	232	520	494	229
Std. deviation	337	219	3268	509	129
Minimum	221	20	84	123	30
Maximum	1164	893	11865	1706	413

Table 3 Temporal evolution pattern of BDNF plasma levels during the perioperative period in patients receiving thiopental/isoflurane anesthesia

Thiopental/isoflurane ($n = 13$)	T1	T2	T3	T4	T5
Mean	549	597	780	708	253
Median	353	466	549	508	179
Std. deviation	512	471	774	701	250
Minimum	132	296	22	187	39
Maximum	2110	1991	2546	2912	973

Duration of surgery varied between 60 and 180 min in the propofol group and between 30 and 240 min in the thiopental–isoflurane group. In the propofol group, there was some evidence of a weak, but statistically significant positive correlation between the duration of surgery and BDNF values at skin closure ($R^2 = 0.38$, $P = 0.026$; Fig. 3a). No such correlation could be found in the thiopental–isoflurane group at skin closure ($R^2 = 0.001$, $P = 0.923$; Fig. 3b). There was no correlation either between the duration of surgery and BDNF plasma concentrations at subsequent time points (i.e. in the post-anesthetic care unit or at 24 h postoperatively).

Discussion

Three main results are emerging from this study. First, in males undergoing elective minor surgery, pre-, intra- and postoperative BDNF plasma kinetics follow a specific pattern. Second, BDNF plasma kinetics are influenced by anesthetic drugs and, possibly, by the duration of surgery. Third, even in a homogenous cohort and a well-controlled clinical setting, BDNF plasma concentrations show large variability.

We focused on plasma BDNF concentrations. In the human blood, average BDNF levels are about 100-fold higher in the serum than in the plasma [7, 8]. This difference is due to the large amount of BDNF that is stored in circulating platelets that degranulate during the clotting process when obtaining serum [9, 10]. Given that BDNF

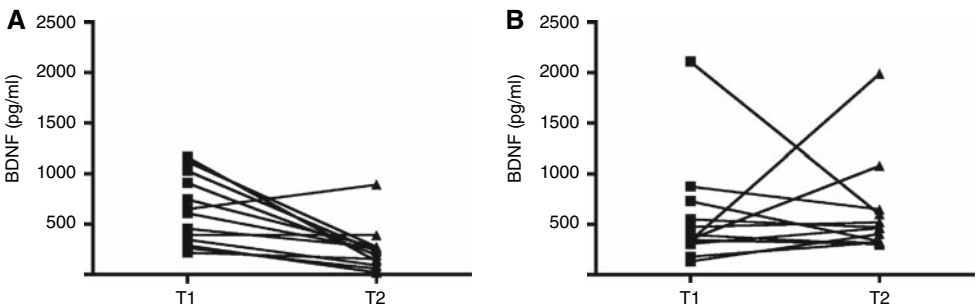

Fig. 2 Short-term evolution of BDNF plasma levels in patients receiving either propofol (**a**) or thiopental/isoflurane (**b**) anesthesia. T1 = baseline (before induction); T2 = 15 min following anesthesia induction

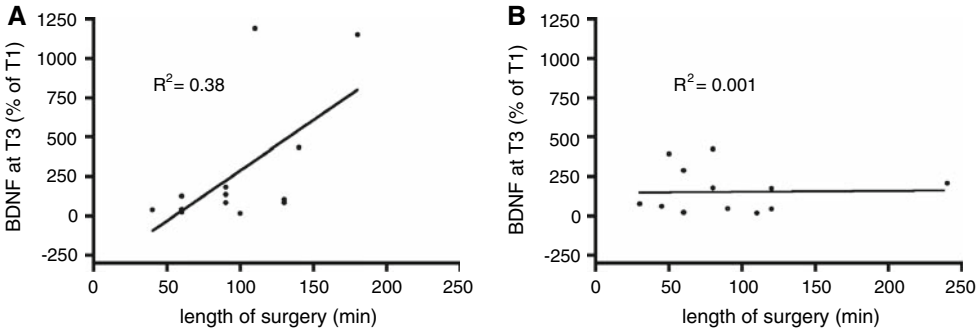

Fig. 3 Correlations between plasma BDNF levels at the end of surgery (T3) and the duration of surgery in the propofol (**a**) and in the thiopental/isoflurane (**b**) group. BDNF values at T3 are expressed as the percentage of initial BDNF levels (T1) of the given individual

secreted by the human brain rapidly crosses the blood-brain barrier [13], we believe that the small amount of BDNF that is detected in the plasma reflects more reliably, at least in theory, acute changes of BDNF secretion in the brain. However, as BDNF is also produced and secreted by non-neuronal cell types [11, 12], it cannot be excluded that the observed changes in BDNF plasma concentrations reflect secretion of this protein from extracerebral sources. Finally, despite the lack of experimental evidence, effects of anesthetics on BDNF uptake and release by platelets cannot be ruled out.

We observed a large variability in BDNF plasma concentrations throughout the study period. At the end of surgery, for instance, when the variability was maximal, interindividual plasma concentrations varied by a factor of more than 100. Important interindividual variability of BDNF plasma concentrations has been described before [8, 26], and subjects' age, weight and gender have been shown to have an impact on this variability [7]. We were unable to identify patients' characteristics that explained this variability. This may have been due to the careful selection of a homogenous, normal-weight, male cohort. However, there was evidence of a statistically significant, albeit weak, positive correlation between the duration of the surgical procedure and BDNF plasma concentrations. This correlation was not fully convincing, since the correlation coefficient was low, the correlation was statistically significant only in patients receiving propofol but not in those receiving thiopental–isoflurane, and at skin closure only but not thereafter. However, it is plausible that longer surgical procedures induce a more pronounced stress response, and, subsequently, higher BDNF plasma concentrations through an increased synthesis of BDNF, a shift of BDNF from the central to the peripheral compartment, a combination of both, or yet another, not yet known mechanism. Finally, it cannot be excluded that the higher BDNF plasma concentrations in patients undergoing longer procedures were related to the prolonged administration of the anesthetic drugs.

We have chosen the time point immediately before induction to measure baseline BDNF plasma concentrations. There were no differences in baseline concentrations between groups. However, average baseline values appeared to be higher compared with data from healthy volunteers in previous reports [7, 8, 26]. There are several possible explanations for this discrepancy. First, although patients in our study were premedicated with a benzodiazepine, it cannot be excluded that in some, preoperative anxiety and stress levels were still significant. In experimental models, acute stress has been shown to result in a rapid upregulation of BDNF mRNA and protein levels in the hypothalamo–hypophyseal stress axis [27], and in the hippocampus [28]. Second, some of the patients may have suffered preoperatively from radicular pain, and this may explain higher baseline BDNF values. However, in one experimental study, chronic pain appeared to reduce, rather than to increase, cerebral BDNF levels [29]. Third, baseline measurements were taken immediately after insertion of a peripheral venous catheter. This procedure can be painful in some patients; in one randomized trial, for instance, 20% of patients reported a pain intensity of 5 or more on a 10-point scale when a 18G catheter was inserted on the back of a hand and without a local anesthetic [30]. Whether BDNF plasma concentrations are changing within seconds after a painful stimulus remains to be determined. Finally, it cannot be excluded that technical issues in blood sampling and measurements, for instance, the use of different ELISA kits, account for the differences between our data and previous observations.

Perhaps the most striking observation was the decrease in BDNF plasma concentrations in the propofol group at 15 min. At this time point, patients were exposed to general anesthesia only; surgery has not yet commenced. The study was well controlled; except for induction and maintenance agents, patients received identical pharmacological treatments. Due care was taken to maintain Bispectral Index within a narrow range. Thus, we may assume that the decrease in BDNF plasma concentrations in the propofol group at 15 min was directly related to the administration of propofol, or the absence of thiopental–isoflurane, or both. Anesthetics are known to cause profound depression of neuronal activity; the important role of

activity-dependent rapid release of BDNF from its intracellular stores in order to promote appropriate neuronal network function has been described [22, 23]. Propofol may influence BDNF secretion in the CNS through $GABA_A$-independent mechanisms. Alternatively, propofol may interfere with the rate of BDNF uptake or release by platelets and the impact of propofol on non-neural BDNF secretion from peripheral organs cannot be excluded either. While propofol, thiopental and isoflurane all enhance inhibitory GABAergic neurotransmission [31], differences in pharmacokinetic and dynamic exist between these drugs and these differences may also explain, at least in part, differences in BDNF plasma concentrations after 15 min. Clearly, further laboratory and clinical research is needed to answer these questions.

Between the 15th minute and skin closure, no further measurements were performed. Thus, we do not know whether BDNF plasma concentrations in the propofol group would have decreased further and at what time point they were eventually back to baseline values.

Twenty-four hours after surgery, we found a significant decrease in plasma BDNF concentrations compared with baseline in both groups. This suggests that in our study population, stress levels, or other mechanisms that increase BDNF levels, were lower at 24 h after surgery than immediately before induction of anesthesia. Our last measurement was at 24 h. We cannot exclude that subsequent measurements would have shown even lower plasma concentrations. Low plasma BDNF concentrations in the postoperative period may reflect anesthesia-related long-term changes in the production of this protein. It has been shown that general anesthesia can induce persistent changes in gene expression in the CNS [32]. It remains to be shown, whether exposure to anesthesia induces long-term changes in BDNF expression. Alternatively, decreased plasma BDNF values could reflect the long-term effects of anesthesia on vascular endothelia, peripheral organs and on platelet function.

Our study has limitations and the results are raising important questions that may inform the research agenda. We included a limited number of well-selected, males undergoing one type of minor surgery. Future investigations may focus on larger and more heterogeneous cohorts that allow for appropriate subgroup analyses, to study, for instance, the impact of gender or of different surgical settings on BDNF kinetics. More work is required to investigate BDNF plasma kinetics in patients undergoing major surgery. Our time window may have been too narrow to adequately document perioperative BDNF kinetics. To obtain an adequate baseline, the first measurement should be done longer before surgery, perhaps in ambulatory patients who are not yet submitted to pre-surgical anxiety and stress. The last measurement needs to be taken longer after the end of surgery to ensure complete recording of BDNF kinetics. The differential effect of propofol and thiopental–isoflurane on BDNF kinetics needs to be elucidated. Also, whether changes in plasma BDNF concentrations reflect altered BDNF secretion in the CNS or other mechanisms remains to be determined. Finally, given the important role of BDNF in higher order cognitive functions [4], the possibility of an association between low BDNF plasma levels and the extent of postoperative cognitive deficits should be evaluated.

In conclusion, in healthy males undergoing elective minor surgery, pre-, intra- and postoperative BDNF plasma concentrations follow a specific pattern. In the early period of propofol anesthesia, and in the absence of surgery, BDNF plasma concentrations are significantly decreased. Reasons for this decrease remain unknown. The large variability in plasma concentrations throughout the perioperative period precludes prediction of BDNF values in individual patients. Future studies should elucidate reasons for this variability.

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