

Block-dependent sedation during epidural anaesthesia is associated with delayed brainstem conduction

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Background. Neuraxial anaesthesia produces a sedative and anaesthetic-sparing effect. Recent evidence suggests that spinal cord anaesthesia modifies reticulo-thalamo-cortical arousal by decreasing afferent sensory transmission. We hypothesized that epidural anaesthesia produces sensory deafferentation-dependent sedation that is associated with impairment of brainstem transmission. We used brainstem auditory evoked potentials (BAEP) to evaluate reticular function in 11 volunteers.

Methods. Epidural anaesthesia was induced with 2-chloroprocaine 2%. Haemodynamic and respiratory responses, sensory block level, sedation depth and BAEP were assessed throughout induction and resolution of epidural anaesthesia. Sedation was evaluated using verbal rating score (VRS), observer's assessment alertness/sedation (OAA/S) score, and bispectral index score (BIS). Prediction probability (P_K) was used to associate sensory block with sedation, as well as BIS with other sedation measures. Spearman's rank order correlation was used to associate block level and sedation with the absolute and interpeak BAEP latencies.

Results. Sensory block level significantly predicted VRS ($P_K=0.747$), OAA/S score ($P_K=0.748$) and BIS. BIS predicted VRS and OAA/S score ($P_K=0.728$). The latency of wave III of BAEP significantly correlated with sedation level ($\rho=0.335$, $P<0.01$) and sensory block ($\rho=0.394$, $P<0.01$). The other BAEP parameters did not change during epidural anaesthesia. Haemodynamic and respiratory responses remained stable throughout the study.

Conclusions. Sedation during epidural anaesthesia depends on sensory block level and is associated with detectable block-dependent alterations in the brainstem auditory evoked responses. Sensory deafferentation may reduce CNS alertness through mechanisms related to brainstem neural activity.

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Subarachnoid and epidural anaesthesia reduce hypnotic requirements for midazolam,^{1,2} thiopental,³ and isoflurane.⁴ For example, high thoracic lidocaine epidural anaesthesia produces a 50% MAC-sparing effect for sevoflurane,⁵ whereas bupivacaine spinal anaesthesia is associated with sedation that increases as a function of block height.^{2,6} These findings were confirmed by others who found that spinal anaesthesia is accompanied by significant sedation, although unrelated to the block height.⁷

The afferentation theory proposes that tonic sensory and muscle-spindle activity modulate cerebral activity and maintain a state of wakefulness.^{8,9} Activation of the EEG in animals

after increasing muscle afferent activity^{8,9} is associated with an increase in cerebral blood flow that exceeds metabolic demand.⁹ On the other hand, temporary peripheral denervation decreases the excitability of cuneate nucleus in the brainstem,¹⁰ while acute block of tonic retinal discharges produced synchronization of the cortical EEG, which was otherwise desynchronized.¹¹ More recent findings suggest that a spinal depressant action of isoflurane¹² or lidocaine¹³ on ascending somatosensory transmission can modulate reticulo-thalamo-cortical arousal mechanisms. Accordingly, a decrease in tonic afferent input, as during neuraxial anaesthesia, would be expected to reduce the level of consciousness.

As with most cranial nerves,¹⁴ secondary auditory neurons, travelling in the medial lemniscus toward the inferior colliculus, are anatomically and functionally related to the reticular formation.¹⁵ These connections form the anatomical background for an extensive interaction between the auditory pathway and reticular formation.^{16–18} In addition, the nucleus of inferior colliculus, an obligatory station of the auditory pathway, receives somesthetic input from the spinothalamic tract and medial lemniscus,^{19, 20} while it appears to induce cortical activation by acting through both cholinergic and serotonergic systems.²¹ Thus, neuronal events such as reduced afferent somatosensory transmission that could affect the excitability of reticular formation would change the character of the brainstem auditory response.

General anaesthetics^{22–25} and sedatives²⁶ have a small but significant effect on brainstem auditory evoked potentials (BAEP) in humans. This effect is mainly associated with increased latencies of the auditory responses; however, its exact mechanism is not fully elucidated. We believe this impairment in brainstem conduction is partly the result of indirect anaesthetic-induced deafferentation of somatosensory transmission. We tested the hypothesis that epidural anaesthesia with chloroprocaine produces block-dependent sedation that is associated with an impairment of brainstem auditory evoked responses.

Methods

With approval from the University of Louisville Human Studies Research Committees and written informed consent, we studied 11 healthy volunteers. None had taken any drug acting on the central nervous system for at least 24 h before the study. Age was restricted to between 18 and 45 yr.

Protocol

Volunteers fasted for at least 8 h before the study. All the standard monitors, the bispectral index (BIS) of the EEG (A-2000, XP platform, Aspect Medical Systems, Inc., Newton, MA, USA), and BAEP monitoring were applied to the participating volunteers, who were resting supine in a warm and quiet environment. An 18-G catheter was inserted into an antecubital vein of the non-dominant arm, and a bolus of 500 ml of Ringer's lactate solution was administered.

An epidural catheter was inserted into the L3–4 interspace and a 15 ml bolus of 2-chloroprocaine 2% was administered after a 15 min control period. Additional 10 ml boluses were given every 10 min until a sensory block near T5 was produced, or a total chloroprocaine dose of 1 g was given. The extent of the block was assessed at 10 min intervals until its total regression and the clinical recovery of all the sensory functions. Volunteers were maintained normothermic throughout the study using forced-air covers.

BIS, observer's assessment alertness/sedation (OAA/S) score, verbal rating score (VRS) for sedation, BAEP and

block level were evaluated (in that order) and recorded 10 min before (baseline) and 10 min after the epidural injection of 2-chloroprocaine, and at 10 min intervals thereafter. An investigator blinded to the extent of the sensory block performed all the assessments. The trial did not exceed 5 h.

Measurements

Characteristics of the volunteers, as well as the total dose of chloroprocaine administered during the trial were recorded. Heart rate, ventilatory frequency, end-tidal carbon dioxide, and pulse oximeter saturation were measured continuously and recorded at 10 min intervals. Blood pressure was determined non-invasively every 5 min and recorded at 10 min intervals with the other measurements. Tympanic membrane temperature was measured at 30 min intervals throughout the study.

Sensory block was evaluated at baseline and at 10 min intervals after the first epidural administration of chloroprocaine, using the response to ice and pinprick, not only bilaterally but also to the cephalad and caudal directions. The total number of blocked dermatomes was recorded for further analysis. At 10 min intervals, BIS, sedation scores, BAEP, and block level were evaluated and recorded in that order. During assessment of the electrophysiological indices, volunteers were advised to relax and keep their eyes closed.

BIS data were gathered using four sensors arranged in frontal-temporal montage after mild abrasion of the skin. Impedance of the sensors was evaluated at 10 min intervals and kept less than 5 k Ω . The smoothing window for BIS was set at 30 s. The volunteers were instructed to close their eyes and lowest BIS value in a 3 min monitoring period was recorded for analysis. During this observation period, special care was taken to maintain a signal quality index (SQI) >50%. Sedation was assessed by a blinded investigator using the responsiveness component of the OAA/S score²⁷ (Table 1). The volunteers simultaneously evaluated their own degree of sleepiness using a VRS for sedation/sleepiness (VRS, 0=wide awake to 10=asleep).

The Neurodiagnostics Laboratory of the University of Louisville Hospital participated in the evaluation of the BAEP. Brainstem responses were obtained from gold cup electrodes placed on the vertex (Cz) and at right and left ear lobes (A1, A2) with a ground electrode placed at mid-forehead (FPz). Two thousands broad-band binaural click stimuli were delivered by the auditory evoked potential

Table 1 Responsiveness component of the Observer's Assessment of Alertness/Sedation (OAA/S) score

Score	Responsiveness
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is spoken loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Does not respond to mild prodding or shaking

module of a Nicolet Viking Select monitor via earphones inserted in the external aural canals (Nicolet Biomedical Inc., Madison, WI, USA). A stimulus rate of 11.11 Hz was used at an intensity of 70 dB above the hearing threshold. Generated stimuli were 100 μ s-long square waves of rarefaction polarity. The recording was triggered at stimulus onset and continued for 10 ms. The monitor used a 50–3000 Hz band pass and a 100 ms time base. Each set of 2000 stimuli was repeated and both traces were superimposed to ascertain the reproducibility of the waves. Masking was used in the non-test ear at 35 dB below the click intensity used in the test ear. This condition allowed well-defined waves to be obtained for measuring the absolute latencies and amplitudes of waves I, III, and V. Interpeak latencies I–V, I–III, and III–V were also obtained. The evaluations of BAEP and detection of the various waves were done by an experienced laboratory technician who was not aware of the study hypothesis, outcomes, or block level.

Data analysis

Mean arterial pressure, heart rate, ventilatory frequency, core temperature, oxygen saturation, and end-tidal carbon dioxide measurements were averaged over the study period and presented as mean (SD) for each volunteer separately.

To measure the strength of the association between level of sensory block and the different measures of sedation—VRS, OAA/S score, and BIS—the prediction probability P_K , was calculated. P_K is the probability that an indicator correctly predicts the depth of sedation.²⁸ The P_K in this case is thus the estimate of the probability that sensory block level will correctly predict sedation depth as expressed by VRS, OAA/S, or BIS. An indicator with a perfect predictive ability has a P_K value of 1.0, whereas an indicator that performs no better than chance has a P_K value of 0.5. In addition, values of VRS and BIS at the same block level were compared in the same

subject between the evolution and regression phase of epidural anaesthesia, using paired *t*-tests. The purpose of this analysis was to examine the possible confounding effect of systemically absorbed chloroprocaine on sedation depth.

The level of sedation expressed by VRS and BIS was graphically presented as a function of sensory block. The latter was categorized in five 5-dermatome groups (0, 1–5, 6–10, 11–15, 16–21).

The level of sensory block, VRS and OAA/S scores, and BIS were correlated with the latencies and amplitudes of the different BAEP using Spearman's rank correlation test. Correlations were first calculated for each volunteer and then averaged across all volunteers. As many correlations were calculated, we considered $P < 0.01$ to be statistically significant. In addition, for the latencies of the three main BAEP—I, III, and V—a graph was constructed to show the change in that parameter between baseline (no block) and maximum block extension (maximum block) for each volunteer. In the case that 'maximum block' was maintained for more than one assessment, the latency data were averaged within the volunteers. Pseudo-paired *t*-tests were used to compare BAEP values between the above two block states.

Results are expressed as mean (SD), unless otherwise noted; differences were considered statistically significant when $P < 0.05$, unless otherwise noted.

Results

The volunteers' characteristics are summarized in Table 2, along with total chloroprocaine dose, core temperature, and circulatory and respiratory function. Volunteer 3 (Table 2) had an episode of hypotension (systolic blood pressure of 75 mm Hg) that lasted for about 3 min and resolved after an infusion of 500 ml of fluid. Otherwise, all haemodynamic and respiratory values remained unchanged during the trial.

Table 2 Volunteer characteristics, epidural chloroprocaine dose and physiological values. Data are presented as mean (SD). The total 2-chloroprocaine (2-CP) dose administered in the epidural space during the trial is presented for each subject separately as mg kg⁻¹ body weight. Non-invasive mean arterial pressure (MAP), heart rate (HR), ventilatory frequency (VF), haemoglobin oxygen saturation (Sp_{O_2}), end-tidal carbon dioxide (E'_{CO_2}), and tympanic membrane temperature (Core temp) were averaged for each volunteer separately across the different sampling points during the trial and across the 11 volunteers. In volunteer 8 we were unable to obtain valid measurements of the tympanic membrane temperature

Volunteer	Gender (M/F)	Age (yr)	Weight (kg)	Height (cm)	2-CP dose (mg kg ⁻¹)	MAP (mm Hg)	HR (beats min ⁻¹)	VF (bpm)	Sp_{O_2} (%)	E'_{CO_2} (mm Hg)	Core temp (°C)
1	M	20	75.9	177.5	12.5	88 (3)	57 (7)	18 (4)	98 (1)	44 (2)	37.0 (0.2)
2	M	25	82.7	165.0	12.0	88 (6)	89 (6)	22 (2)	100 (1)	39 (4)	37.8 (0.5)
3	M	28	65.0	180.0	12.9	72 (14)	72 (6)	17 (5)	99 (2)	43 (3)	36.7 (0.3)
4	M	40	81.8	175.0	11.2	105 (13)	72 (6)	18 (3)	97 (1)	43 (3)	37.1 (0.3)
5	M	24	90.9	177.5	10.8	107 (4)	70 (6)	18 (3)	99 (1)	42 (2)	37.4 (0.1)
6	M	25	93.0	182.5	9.4	91 (3)	71 (6)	18 (3)	100 (0)	43 (3)	36.8 (0.4)
7	F	28	65.5	172.5	14.7	89 (3)	83 (7)	18 (4)	100 (1)	43 (1)	36.9 (0.3)
8	F	27	98.0	170.0	5.3	96 (8)	80 (4)	18 (3)	99 (1)	41 (2)	–
9	M	33	85.5	185.0	8.4	99 (3)	69 (9)	17 (4)	99 (1)	38 (3)	37.3 (0.0)
10	F	22	54.5	160.0	11.7	86 (5)	74 (6)	18 (4)	100 (0)	47 (2)	37.4 (0.0)
11	M	30	59.0	177.5	14.6	74 (7)	68 (5)	17 (3)	99 (1)	43 (2)	36.7 (0.0)
Mean (SD)	8/3	27 (6)	77.0 (15)	175.0 (7)	11.2 (2.7)	91 (13)	74 (11)	18 (4)	99 (1)	42 (3)	37.1 (0.4)

Table 3 Prediction probability estimates. * $P < 0.01$ was considered statistically significant for this analysis because multiple statistical comparisons were performed. Prediction probability (P_K) values of the sensory block, determined by pinprick (Block_p) or temperature (Block_t), for the verbal sedation (VRS, 0–10) and observer's assessment alertness/sedation (OAA/S) scores, and BIS. P_K values of BIS for the VRS and OAA/S scores are also presented. The statistical test here compares the P_K value with 0.50, which is the P_K value that represents no association

	P_K for VRS	P_K for OAA/S score	P_K for BIS
Block_p level	0.747*	0.748*	0.594*
Block_t level	0.670*	0.662*	0.507
BIS	0.662*	0.728*	–

Table 4 Correlations between brainstem auditory evoked potentials (BAEP), sensory block level and BIS. * $P < 0.01$ was considered significant. Spearman's rank correlations were first calculated for each volunteer separately and then averaged across all volunteers. One-sample t -test was used to determine which of the average correlations were significantly different from zero

BAEP	VRS (0–10)	Block_t level	Block_p level	BIS
I Lat	0.079	0.110	0.124	0.036
III Lat	0.335*	0.394*	0.360*	–0.079
V Lat	0.194	0.273	0.289	–0.031
I–III IPL	0.122	0.179	0.138	–0.133
III–V IPL	0.016	0.061	0.138	–0.008
I–V IPL	0.079	0.189	0.104	–0.022
I Amp	–0.013	0.038	0.189	0.096
V Amp	0.045	0.063	0.043	0.002

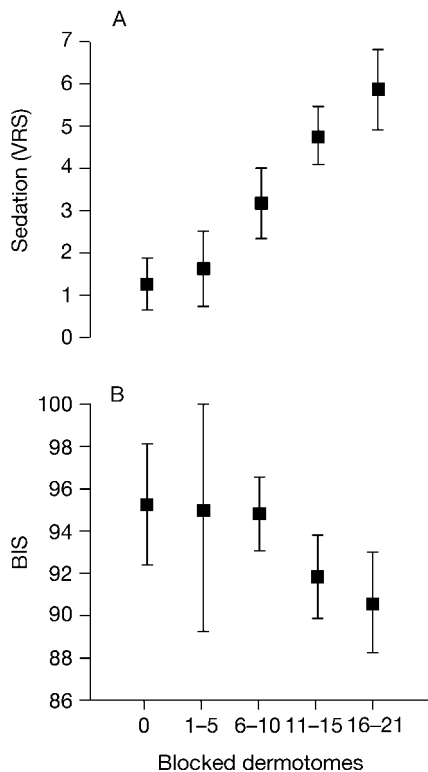


Fig 1 Level of sedation, expressed by (A) verbal rating score (VRS), and (B) bispectral index (BIS), as a function of the sensory block. The latter was categorized in 5-dermatome groups. Data are presented as means with 95% confidence intervals.

Poor signal quality ($\text{SQI} > 50\%$) did not allow us to collect useful BIS data for further analysis in three of 11 volunteers.

Prediction probability, P_K , estimates showed that the level of sensory block predicted sedation depth as measured by VRS and the OAA/S score (Table 3). The P_K value of sensory block level to predict BIS was small, but still significantly different from 0.50 (0.50 indicates no association). Paired analysis showed that sedation depth, as evaluated by VRS and BIS, was the same between the evolution and regression of the block for the same block level. The level of sedation, expressed by VRS and BIS, is presented graphically as a function of sensory block in Figure 1.

Spearman's rank correlation tests showed statistically significant associations between the VRS and block level and the latency of wave III from the BAEP (Table 4). The correlation of wave V latency did not reach statistical significance ($P > 0.01$). Graphical presentation and analysis also showed a significant increase in the latency of wave III at maximum block extension state compared with baseline (no block, $P < 0.05$), whereas latencies of I and V remained unchanged (Fig. 2).

Discussion

Experimental evidence suggests that various types of anaesthetics indirectly suppress cortical responses to painful or other ascending stimuli by an action on the spinal cord.²⁹ The mechanism for this effect is not completely understood, but compelling evidence exists that spinal cord anaesthesia, through a decrease in the ascending somatosensory transmission, depresses the activity of reticulo-thalamo-cortical mechanisms that regulate arousal.^{12 13} On the other hand, acute sensory deafferentation in various animal models is associated with reduced activity of the midbrain reticular formation and cerebral cortex.^{10 11} In humans, epidural and spinal anaesthetics depress consciousness and reduce anaesthetic requirements for different anaesthetic endpoints.^{1-3 5 7} However, resetting the brain's arousal system by deafferentation of sensory input implies a dose-dependent effect—which has not previously been clearly demonstrated.

Sensory block level during epidural anaesthesia significantly predicted sedation depth in our volunteers, as measured by both objective and subjective methods. Loss of afferent sensory input during epidural anaesthesia was associated with a downregulation of brainstem neural activity as this was evaluated using BAEP. The latency of BAEP III showed a significant correlation with the level of sensory block. Wave III is generated by neural elements around the nucleus of inferior colliculus, which receives somesthetic input from the spinothalamic tract and medial lemniscus,^{19 20} while it appears to induce cortical activation by acting through both cholinergic and serotonergic systems.²¹ Auditory

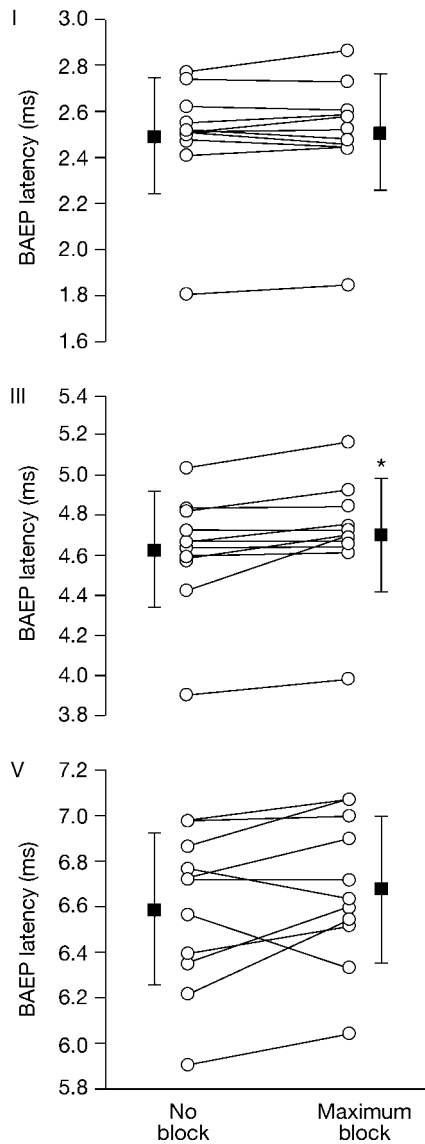


Fig 2 Latencies of I, III, and V BAEP for each volunteer at baseline (No block) and maximum block extension (Maximum block) during the trial. If ‘Maximum block’ was maintained for more than one assessment, the latency data were averaged within the volunteers. Pseudo-paired *t*-test showed a significant increase only in the latency of wave III (**P*=0.015).

circuits in the brainstem interact with reticular nuclei providing the anatomical basis for the defence alertness reaction, sensory information control, and even sleep regulation.^{17 18}

Taken into account the very limited BAEP response to general anaesthetics,^{22–25} even at anaesthetic depths associated with EEG burst suppression,³⁰ believe that the significant correlation of sensory block with the latency of brainstem potential III involves a selective effect of sensory deafferentation on the activity of the midbrain region inside and in the vicinity of inferior colliculus. Despite the fact that sensory input (including auditory stimulation) from the unblocked areas of the body might have counteracted any

deafferentation effect on BAEP in unmedicated volunteers, brainstem conduction showed a significant positive correlation with the block level and sedation depth. These findings support the original hypothesis that sensory block affects, in a dose-dependent manner, brainstem transmission.

The effect of epidural anaesthesia on BAEP has been evaluated previously by others³¹ who found that lidocaine epidural anaesthesia prolonged the peak latencies and delayed brainstem transmission. However, a similar pattern of BAEP inhibition after i.v. lidocaine administration³² suggested that systemic absorption rather than anaesthetic block itself was responsible for the effect on brainstem neural activity. To avoid the potential effect of systemically absorbed anaesthetic on BAEP, we used chloroprocaine, which is metabolized by plasma cholinesterase and has an elimination half-life ranging from 10 s to 3 min.^{33 34} Using multiple small epidural boluses enabled us to assess the sensory block level during its evolution, as well as its regression. Comparison of sedation depth at the same block between those two phases of the anaesthetic did not reveal any difference. Thus, despite our lack of a placebo-controlled experimental condition, we believe that repetitive assessments of the block level, during both evolution and regression of the sensory block, reduced the likelihood that systemic chloroprocaine or elapsed study time confounded our findings.

As the activity of cholinesterase in the cerebrospinal fluid (CSF) is greatly diminished compared with the plasma,³⁵ there still remains a theoretical possibility that part of the chloroprocaine absorbed into the CSF could flow in the cephalad direction and exert its effects directly on the brainstem. However, in that case, a homogeneous rather than selective effect on BAEP would be a more likely outcome. Our findings do not support this possibility.

Responsiveness of the volunteers was maintained at an OAA/S score of 4 or 5. These data are in agreement with previous findings.⁷ Prediction probability analysis showed that sensory block level predicts OAA/S score with similar strength as VRS. P_K is a non-parametric measure of association that is recommended as a performance measure for anaesthetic depth indicators and observed depth scales of any degree of coarseness or fineness.²⁸ It is important to understand that the P_K statistic is not prediction as we typically think of it. Instead, P_K is the probability that for any two data pairs selected from the data set, the order of one variable (e.g. block level) will correctly ‘predict’ the order of the other variable (e.g. VRS). In a sense, the P_K value is the proportion of times that the higher VRS score is paired with the higher block level. We believe that the use of self-reported sedation did not introduce bias in our results because the volunteers were not aware of the purpose of the study or the basic hypothesis. Consistent with this theory, P_K values of sensory block level were identical for the VRS and OAA/S score.

The BIS predicted sedation depth as defined by the VRS and OAA/S score. The P_K value of sensory block level for BIS was lower than for the other sedation depth indicators; however, it was significantly different from 0.50, which is the

P_K value indicating no association. This is a new finding and contrasts with results of a previous placebo-controlled trial, which concluded that BIS was an insensitive indicator of sedation and was affected only 60 min after the injection of spinal anaesthetic.⁷ This late sedation was ascribed to delayed cephalad spread of the local anaesthetic. On the other hand, in a non-randomized trial, the same investigators found that the largest deviation of BIS from the baseline value occurred 30 min after spinal injection and coincided with the highest block level.⁷

In conclusion, we found that sedation during epidural anaesthesia depends on the level of sensory block and is associated with detectable alterations in the brainstem auditory evoked responses. Sensory deafferentation during neuraxial anaesthesia may modulate CNS alertness through mechanisms related to brainstem neural activity.

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