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Original Article

Stress-related biomarkers of dream recall and implicit memory under anaesthesia*

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Summary
The aim of this study was to investigate whether auditory presentation of a story during general anaesthesia might influence stress hormone changes and thus affecting dream recall and/or implicit memory. One hundred and ten patients were randomly assigned either to hear a recording of a story through headphones or to have routine care with no auditory recording while undergoing laparoscopic cholecystectomy. Anaesthesia was standardised. Blood samples for cortisol and prolactin assays were collected 20 min before anaesthesia and 5 min after pneumoperitoneum. Dream recall and explicit/implicit memory were investigated upon awakening from anaesthesia and approximately 24 h after the end of the operation. Auditory presentation was associated with lower intra-operative serum prolactin concentration compared with control (p = 0.0006). Twenty-seven patients with recall of dreaming showed higher intra-operative prolactin (p = 0.004) and lower cortisol (p = 0.03) concentrations compared with those without dream recall. The knowledge of this interaction might be useful in the quest to ensure postoperative amnesia.

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Incomplete abolition of cognitive faculties such as memory and learning during anaesthesia has been studied for many years [1–8]. Interestingly, in most cases anaesthetic drugs cause obliteration of explicit memory, whereas implicit memory and/or dream recall may sometimes be preserved [1–8]. Previous studies have tried to identify the relationship between implicit memory or dream recall and depth of anaesthesia using EEG-derived parameters [1–3, 8]. In this respect, both implicit memory and dream recall have been associated with a high degree of responsiveness of the primary cortex [1–3]. Another area of interest is to identify possible intra-operative factors responsible for memory formation under anaesthesia. Deeprose et al. [7] have shown that an auditory stimulus administered during surgery may improve memory performance. They assumed that this effect might be mediated by stress hormones released because of surgery. According to this theory, the auditory stimulus together with surgical stimulation plays a crucial role in modulating the secretion of stress hormones via the hypothalamic–pituitary–adrenal axis [9] in such a way as to affect memory storage [10, 11]. In this regard, low cortisol levels are considered critical for memory consolidation during slow-wave sleep [12, 13], whereas high levels of prolactin seems to be involved in the improvement of memory performance [14].

It is well known that surgical stimulation under deep general anaesthesia is associated with low cortisol and high prolactin levels [15]. On the other hand, to the best of our knowledge, the relationship among auditory stimulus, stress-related biomarkers and memory formation during general anaesthesia has not been studied previously. The hypothesis of this study was that an auditory presentation of a story during anaesthesia might affect cortisol or prolactin secretion and this, in turn, might increase the chance of dream recall and/or implicit memory.

Methods

The study was carried out at Agostino Gemelli Hospital in Rome with approval from the local Research Ethics Committee. Patients undergoing elective laparoscopic cholecystectomy were recruited after providing written consent. Subjects were aged between 18 and 70 years with ASA physical status 1–2. Exclusion criteria comprised psychiatric, neurological and hearing disorders, body mass index (BMI) > 30 $kg.m^{-2}$, addiction to drugs or alcohol, level of education below completion of high school, language comprehension problems, treatment with corticosteroids and/or oestrogens, disorders of the adrenal cortex or prolactin secretion, pregnancy, lactation or postmenopausal hormone therapy.

Patients were assigned in a randomised double-blind manner to an auditory presentation group who had a taped recording played through headphones during surgery and a control group. The random number sequence was generated by a software program and transcribed to consecutively numbered sealed envelopes. Patients from the auditory presentation group were presented with the recording from the time of surgical incision, whereas patients in the control group were isolated from any sounds using specific headphones (30 db Peltor Optime; 3M, Berkshire, UK). One of two 9-min recordings was played to patients in the auditory presentation group via an MP3 player (Samsung YP-U2R, Milan, Italy), depending on whether the randomisation code was odd or even. Each recording contained a part of a fairy story, either Pinocchio or Puss in Boots; the story was then followed by four keywords mentioned in the story, each keyword being repeated three times. The entire story-keyword sequence was repeated twice more. The anaesthetist conducting the anaesthetic was blinded to the group allocation and contents of the recordings.

Psychological stress level was measured using the State Trait Anxiety Inventory (STAI), a questionnaire consisting of 40 items that analyse acute state anxiety (STAI Y1) and background trait anxiety (STAI Y2) [16]. The test was performed on the day of surgery, approximately 30 min before induction of anaesthesia.

Patients were not premedicated. Twenty minutes before anaesthetic induction, intravenous access was established with an 18-G cannula. Baseline blood samples were collected for cortisol and prolactin levels. Repeat samples were taken 5 min after achieving a pneumoperitoneum pressure of 12 mmHg. Commercially available chemiluminescence assay kits for the Abbott Architect i1000sr immunologic analyser (Abbott Laboratories, Chicago, IL, USA) were used to measure serum levels of cortisol and prolactin. Bispectral index (BIS; BIS Vista™ monitoring system, Aspect Medical System Inc, Norwood, MA, USA) electrodes were placed on the fronto-temporal region after cleaning the skin with alcohol to achieve an impedance < 5 kΩ. Bispectral index was monitored throughout anaesthesia, including every 3 min during the auditory presentation, and immediately after awakening.

Non-invasive arterial pressure and heart rate recording was started before anaesthetic induction. General anaesthesia was induced with propofol 2 $mg.kg^{-1}$, remifentanil 0.25 $\mu g.kg^{-1}.min^{-1}$ and cisatracurium 0.15 $mg.kg^{-1}$ and maintained with sevoflurane at an end-tidal concentration of 2.2% (MAC 1.0). The remifentanil infusion was adjusted between 0.10 and 0.40 $\mu g\ kg^{-1}.min^{-1}$ to maintain mean arterial pressure and heart rate within 20% of baseline. Postoperative analgesia was provided by intravenous administration of morphine 0.06 $mg.kg^{-1}$ and paracetamol 1 g at the end of surgery. The surgical procedure involved Hasson's open access technique in the 30° reverse Trendelenburg position and intraperitoneal insufflation of carbon dioxide. A mean value for heart rate, systolic blood pressure and diastolic blood pressure during intra-operative auditory presentation was calculated from three consecutive readings.

When the patients opened their eyes at the end of anaesthesia, they were immediately asked whether they recalled any dreams, and if so, were requested to describe the details. Approximately 24 h after surgery, patients were asked a series of open-ended questions to probe explicit recollection of intra-operative events [1–3, 8]: 'What is the last thing you remember before falling asleep?', 'What is the first thing you remember upon awakening?', 'Did you dream while you were asleep?', 'Did you hear any words or sounds while you were asleep?' Implicit memory was investigated using a story-related free association test [1–3, 8].

Patients were played a standard recording of all eight keywords, consisting of four from the story that they had heard plus four from the other story as a control, which was then repeated once. They were invited to say the first thing that came to mind after listening to each word. The test was considered to be positive if the patient heard a keyword from the auditory presentation that had been played during anaesthesia and stated something about it such as the title or a sentence, but without a conscious recollection of the intra-operative recording.

At the end of the interview, explicit recall was assessed by telling patients from the auditory presentation group that they had listened to a recording of a story and asking them whether talking about the stories brought back any memories of having heard a recording during anaesthesia.

Patients who had a sensation of having dreamt during anaesthesia without being able to describe the content and patients who reported a dream for the first time only at the second interview were classed as not having dreamt. The postoperative interview was conducted by an anaesthetist who was blinded to the group assignment and the story that had been played.

The number of patients included in the study was based on a priori power analysis assuming α of 0.05 and a power of 80%. A minimum of 50 patients for each group was required to detect a 25% reduction in hormone levels in the auditory presentation group compared with the control group. The study plan was to recruit 110 patients as the investigators expected a 10% drop-out rate in each group. Factorial ANOVA with two factors (auditory presentation/control; dream recall/no recall) and with intervals as repeated measures was performed on time-related measurements (baseline and intra-operative prolactin and cortisol levels). If differences in the interactive terms (i.e. auditory presentation × dream recall × time) were significant, post-hoc Scheffé tests were undertaken to ascertain the location of the significant effects. To balance sex differences between dreaming and non-dreaming patients, ANOVA was carried out on sex and dreaming for intra-operative prolactin and cortisol levels.

For absolute values, Student's t-test or chi-square test with Yates correction was used as appropriate. The Mann–Whitney U-test was used for BIS values with Bonferroni correction for multiple comparisons. A significance level of $p < 0.05$ was used. Statistical analyses were performed using Statistica Version 5.1 software (StatSoft, Tulsa, OK, USA).

Results

One hundred and ten patients were assessed for eligibility into the study (Fig. 1). After exclusions, 54 patients in the auditory presentation group and 52 patients in the control group were studied. These were comparable in terms of physical characteristics and anaesthetic variables (Table 1).

Baseline hormone concentrations did not differ between groups. Cortisol decreased and prolactin increased intra-operatively in both groups (Table 2). Analysis of variance showed significant effects for auditory presentation ($p = 0.003$), dream recall ($p = 0.002$) and time ($p < 0.0001$) on prolactin levels. A significant interaction effect occurred for auditory presentation and time ($p = 0.0006$) and dream recall and time ($p = 0.004$). Post-hoc analysis revealed that auditory presentation determined lower intra-operative values of prolactin in patients without compared with those with dream recall (Table 2).

Analysis of variance showed a significant effect for dream recall ($p = 0.006$), time ($p < 0.0001$) and the interaction between dream recall and time ($p = 0.03$) on cortisol levels. Post-hoc analysis revealed that patients with dream recall had significantly lower values of intra-operative cortisol compared with the patients without dream recall in the group who had auditory presentation (Table 2).

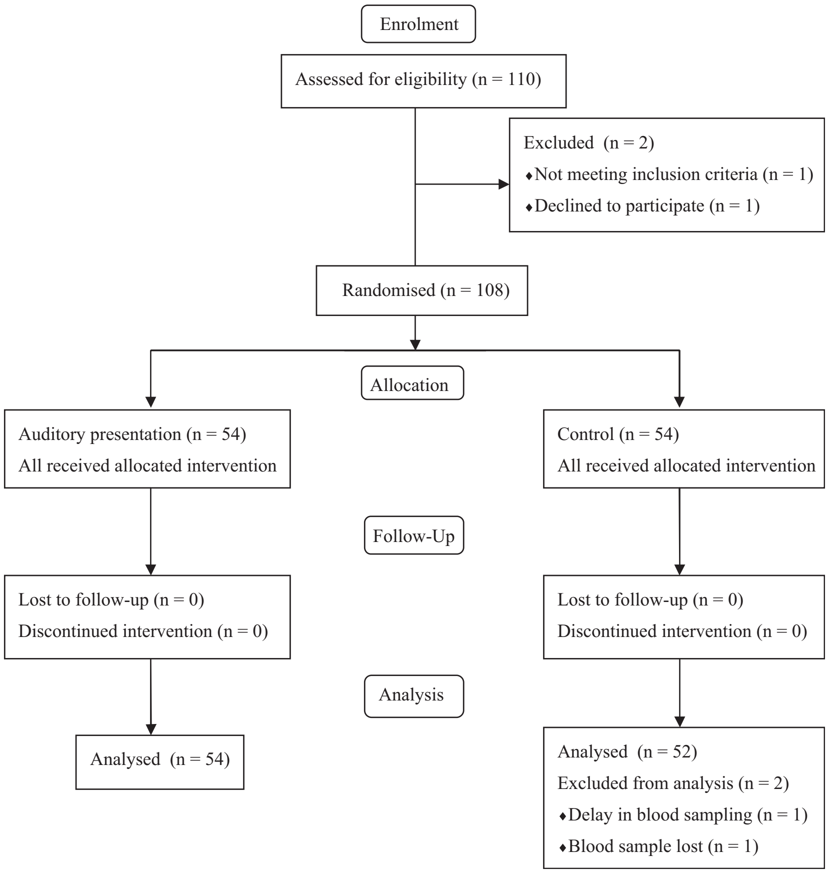

Figure 1 CONSORT flow diagram of patient recruitment.

An effect of sex ($p < 0.0001$) and auditory presentation ($p = 0.003$) was found for intra-operative prolactin levels without significant interaction between sex and auditory presentation ($p = 0.52$), and an effect of sex ($p < 0.0001$) and dream ($p = 0.04$) was found without significant interaction ($p = 0.52$). There were no significant effects of sex for intra-operative cortisol in dreaming vs non-dreaming patients.

None of the patients showed an explicit memory for intra-operative recording. At the first interview, 17 (31%) in the auditory presentation group and 10 (19%) in the control group reported that they had dreamt during anaesthesia ($p = 0.22$), but their reports showed no association with the contents of the recordings presented during anaesthesia. Their dreams were mostly pleasant, characterised by positive emotions and contained references to life events. The characteristics of patients compared with those without dream recall are shown in Table 3.

Three (5.5%) patients who had auditory presentation had implicit memory. Mean (SD) intra-operative prolactin values were 187.9 (16.0) $ng.ml^{-1}$ in patients with and 95.0 (66.4) $ng.ml^{-1}$ in patients without implicit memory.

No differences were found in BIS values during anaesthesia and after awakening between the two auditory presentation groups (Table 1) and between patients with and without dream recall.

Discussion

The main finding of this study was that there was a significantly smaller increase in serum prolactin in patients who had auditory presentation during anaesthesia, but were without postoperative dream recall, compared with the other subsets. Moreover, patients who reported dream recall showed higher values of intra-operative prolactin than those of patients without dream recall, suggesting that prolactin may aid memory storage. The ability of prolactin to activate

Table 1 Characteristics of patients in the auditory presentation and control groups, together with details of anaesthesia. Values are mean (SD) or number (proportion).

	Auditory presentation (n = 54)	Control (n = 52)
Age; years	49.2 (12.8)	48.11 (13.9)
BMI; kg.m^{-2}	25.5 (2.7)	25.2 (2.9)
Sex; male	32 (59%)	21 (40%)
ASA physical status 1/2	38 (70%)/ 16 (30%)	36 (69%)/ 16 (31%)
Duration of anaesthesia; min	86.8 (28.8)	90.3 (25.7)
Total remifentanil dose; μg	835.2 (258.2)	888.5 (382.3)
STAI Y1	44.2 (12.1)	43.7 (11.2)
STAI Y2	35.5 (9.1)	35.6 (7.9)
BIS before pneumoperitoneum	43.6 (7.7)	42.3 (7.1)
BIS 5 min after pneumoperitoneum	42.9 (7.4)	41.9 (6.6)
HR during audio presentation; beats.min^{-1}	65.4 (8.1)	65.9 (9.9)
SAP during audio presentation; mmHg	111.5 (9.0)	110.7 (8.4)
DAP during audio presentation; mmHg	68.3 (5.5)	67.9 (5.3)
Time to open eyes; min	8.6 (2.8)	8.5 (2.4)

BMI, body mass index; STAI Y1, State Trait Anxiety Inventory-state anxiety; STAI Y2, State Trait Anxiety Inventory-trait anxiety; BIS, bispectral index; HR, heart rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure.

the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathways in the hypothalamic region and to stimulate the expression of c-Fos in the supraoptic nuclei [17, 18] suggests a role of this neuropeptide in mediating long-term potentiation of memory formation [19].

A suggested mechanism for the significant difference in prolactin change between the two groups is that auditory stimulation caused a reduction in the depth of anaesthesia and perception of the story as reassuring, hence reducing intra-operative stress. However, intra-operative BIS monitoring did not confirm this interpretation as there were no differences in BIS values between the auditory presentation groups or those with or without dream recall. It is possible that those patients who reported dream recall experienced more intra-operative stress, giving rise to a more marked increase in prolactin. In this regard, our BIS monitoring did not detect periods of light anaesthesia

Table 3 Characteristics of patients with and without recall of dreams. Values are mean (SD) or number (proportion).

	Dream recall (n = 27)	No recall (n = 79)	p value
Age; years	42.5 (11.7)	50.8 (13.2)	0.005
BMI; kg.m^{-2}	24.4 (2.7)	25.7 (2.7)	0.03
Sex; male	9 (33.3%)	44 (55.7%)	0.04
Total remifentanil dose; μg	690.7 (289.2)	919.6 (316.9)	0.001
STAI Y1	49.6 (11.0)	41.8 (11.1)	0.002
STAY Y2	36.4 (8.7)	35.2 (8.5)	0.54
Time to open eyes; min	7.0 (2.1)	9.0 (2.6)	0.0005

BMI, body mass index; STAI Y1, State Trait Anxiety Inventory-state anxiety; STAI Y2, State Trait Anxiety Inventory-trait anxiety.

Table 2 Changes in hormone levels in the auditory presentation and control groups, and the subgroups with or without dream recall. Values are mean (SD).

	Auditory presentation			Control		
	All patients (n = 54)	Dream recall (n = 17)	No recall (n = 37)	All patients (n = 52)	Dream recall (n = 10)	No recall (n = 42)
Prolactin baseline; ng.ml^{-1}	11.8 (16.3)	14.1 (13.8)	10.7 (17.4)	13.6 (11.2)	11.1 (5.8)	14.2 (12.1)
Prolactin 5 min after pneumoperitoneum; ng.ml^{-1}	100.1 (68.0)*	138.9 (74.4)†	82.3 (57.7)†**	145.2 (58.6)*	176.0 (33.6)	137.9 (61.1)**
Cortisol baseline; g.dl^{-1}	11.6 (4.2)	11.0 (5.0)	11.8 (3.8)	11.1 (4.8)	9.9 (3.3)	11.4 (5.1)
Cortisol 5 min after pneumoperitoneum; g.dl^{-1}	8.1 (4.3)	5.2 (3.4)††	9.4 (4.0)††	7.7 (3.4)	5.4 (1.8)	8.3 (3.5)

*$p < 0.0001$; †$p = 0.003$; **$p < 0.0001$; ††$p = 0.0001$.

during which memory circuits might have been activated, as found in other studies [7, 20, 21]. The use of the isolated forearm technique might be an alternative approach to explore this question [22].

Auditory stimulation did not affect cortisol levels. There was a relationship between dream recall and lower cortisol secretion. After post-hoc analysis, this effect remained only in the auditory presentation group. It might be hypothesised that the combination of auditory stimulus and memory formation resulted in lowering cortisol secretion. These results are consistent with other studies showing a relationship between episodic memory deficits and high levels of glucocorticoids. Impaired memory function was found in patient populations with chronically elevated levels of cortisol, such as patients with Cushing's syndrome, major depression and schizophrenia, as well as asthmatic patients [23, 24]. Furthermore, episodic memory may be impaired after the administration of a single low dose of hydrocortisone [25].

The second hormone measurement was made approximately 12 min after the start of surgery. The change in hormone concentration may be secondary to a combination of factors, including surgical approach and reverse Trendelenburg position [26] as well as to drugs used for anaesthesia [15, 27]. The intra-operative hormone assay was performed early in the procedure after standardised skin incision and pneumoperitoneum to avoid the confounding effect of variations in the degree of intra-operative surgical stimulus on stress hormone secretion.

Similar to the findings of Leslie et al., in this study, the incidence of dreaming was 25% [20]. The low rates found in another study were probably related to interviews' being performed late [28]. In previous research [29, 30] as well as in this study, patients who reported dreaming during anaesthesia were younger, had a lower BMI and showed more rapid awakening from anaesthesia. Moreover, higher rates of dreaming were reported by women compared with men. A greater tendency to recall dreams after sleep in women has been attributed to their higher interest in dream content compared with men [29, 30]. The higher rate of dreaming during anaesthesia in younger patients could be due to sleep problems experienced by older people [31]. In this study, patients who dreamt had a larger total dose of remifentanil. This may suggest a role of intra-operative opioids in affecting postoperative dream recall. In addition, our dreaming patients showed higher pre-operative state anxiety scores, which are in contrast to previous studies that did not find a clear correlation of postoperative dream recall with personality trait [20, 29]. In this regard, psychological stress has been found to activate memory in rats [32]. Lastly, arousal occurring sooner may have made patients more likely to recall dreams.

A limitation in the interpretation of our results is that patients who dream were more frequently women; however, the intra-operative increase in prolactin levels in these patients was unlikely to be a sex-related effect. A further limitation is that only three individuals showed implicit memory; this is due to the low incidence of the phenomenon and our study was not powered to draw meaningful conclusions about this outcome [7, 21].

In conclusion, the findings of this study suggest a relationship between lower intra-operative prolactin secretion induced by auditory presentation and memory impairment. The interaction found between external stimuli and the apparent decrease in intra-operative stress should be taken into consideration when establishing a strategy for postoperative amnesia.

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Competing interests

No competing interests declared.

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