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Effect of Preoperative Pregabalin on Induced Hypotension and Postoperative Analgesia with Functional Endoscopic Sinus Surgery

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Abstract

Background: Our target was to estimate the effect of pregabalin as premedication on deliberate hypotension and quality of the surgical site during functional endoscopic surgery for nasal sinuses (FESS) and its postoperative analgesic effect.

Materials and methods: Eighty patients ASA I-II prepared for FESS were included in this randomized research. The study encompassed 2 groups [control group (C) and pregabalin group (P)]. Patients were given either placebo capsule [group (C)] or pregabalin capsule 150 mg [group (P)] 1 h preoperatively. During surgery mean arterial blood pressure (MAP) was maintained between 55-60 mmHg by intravenous infusion of nitroglycerin (NTG) at a rate of 0.5-10 μg/kg/min. We recorded quality of surgical site [using average category scale (ACS)], the overall dose of NTG used, postoperative pain, the overall dose of morphine used postoperatively, and number of patients requesting analgesia.

Results: Pregabalin group (P) showed better ACS, lower overall dose of NTG used, less postoperative pain, lower overall dose of morphine, and less number of patients requesting analgesia than control group (C).

Conclusion: Preoperative oral pregabalin improved the quality of the surgical site during FESS, and decreased the required dose of intraoperative hypotensive agent and postoperative morphine with better postoperative analgesia.

Keywords: Pregabalin; Induced hypotension; Postoperative analgesia; FESS

Introduction

Functional Endoscopic Sinus Surgery (FESS) requires dry surgical area in order for the surgeon to recognize the structure accurately as the anatomical structure of the surrounding area is complicated and the surgical site is near to the eye, brain, cranial base, important vessels and nerves [1]. Excess bleeding leads to defective visibility and causes major complications during FESS [2]. Dry surgical area can be produce by controlled hypotension techniques [3].

Several drugs are used to perform induced hypotension as volatile anesthetics, vasodilators, beta blockers, magnesium sulphate and several medications combinations [4]. Pregabalin belongs to gabapentinoids which includes also gabapentin. Structurally, pregabalin is an analog of γ-aminobutyric acid. It acts on the presynaptic voltage gated calcium channel, reducing the synthesis of neurotransmitter glutamate, leading to antiepileptic, pain killing, and anxiolytic effects.

When given orally, pregabalin reaches its peak level in plasma within 1 h [5]. The target of this research was to estimate the effect of pregabalin (when used preoperatively) on deliberate hypotension and surgical site quality during FESS and its postoperative analgesic effect.

Patients and Methods

This randomized prospective research was executed in ENT department of Tanta University Hospital for 6 months from March 2017 to August 2017 on 80 adult patients (ASA I-II) aged between (18-50) years and prepared for FESS after approval by local ethical committee. Every patient signed a written and informed consent. Research results were used only for scientific purposes.

Patients were randomly located into 2 groups (each 40 patients)

- Control group (Group C) (40 patients).
- Pregabalin group (Group P) (40 patients).

Randomization was carryout using computer generated block randomization to create a list of numbers, each number referred to one group. Then each number was sealed in opaque envelope. Each patient was asked to choose one envelope and give it to the anesthesiologist who compared the number with the list created by computer and accordingly assigned the patient to one group.

Inclusion criteria: Patients were involved in the research if they were prepared for FESS, aged 18-50 years, and had ASA physical status I-II.

Exclusion criteria: Patients were omitted if they had cerebrovascular disease, arterial hypertension, cardiac disease, coagulation defects, history of insufficient kidney or liver functions, or hypersensitivity to the used drugs. All participants were assessed preoperatively by history taking, clinical examination, and laboratory evaluation.

Procedure: One h before surgery all participants in Group P (40), took pregabalin capsule (Amoun pharmaceutical company, Egypt) 150 mg orally with 10 mL of water and all participants in Group C (40) took a similar looking placebo capsule. All given capsules were formulated by the pharmacy. The anesthesiologist, the surgeon, and the participant were blinded to the randomization.

On arrival of the patients to the operative theater, and after placement of ECG, blood pressure, pulse oximetry, temperature probe, bispectral index (BIS) and capnography, intravenous line was inserted and intravenous fluid was started. Intra-arterial catheter was introduced in the radial artery for invasive monitoring of arterial blood pressure. All participants inhaled 100% oxygen for 3 min, then anesthesia started with intravenous injection of Fentanyl (Sunny pharmaceutical, Egypt) (1 µg/kg), Propofol (Astra Zeneca UK) (2 mg/kg), and Atracurium (GlaxoSmithKline, UK) (0.5 mg/kg), then trachea was intubated and patients were mechanically ventilated to keep the end tidal CO_2 values between 34-36 mm Hg. Incremental atracurium doses (0.1 mg/kg) were given every 30 min or when need.

Isoflurane (Kahira pharmaceuticals and chemical industries company, Egypt) 1-2% in 100% oxygen was used to maintain BIS between 40 and 60. Patient was positioned supine with the head up (about 30°C) to improve the venous drainage. A piece of cotton soaked with lidocaine 2% with epinephrine (1:200,000) was placed inside the nose then lidocaine 2% with epinephrine (1:200,000) was injected submucosally.After the patient was anesthetized but before the start of the surgery, nitroglycerin (NTG) infusion was started at rate of 0.5 to 10 µg/kg/min to keep mean arterial pressure (MAP) between 55 and 60 mmHg.

When MAP decreased to 55 mmHg or less, nitroglycerin infusion rate was reduced or stopped, iv fluid 200 ml bolus was given, isoflurane was decreased and 5 mg of ephedrine was injected if MAP still less than 55 mmHg. If heart rate (HR) decreased to <50 beat/min, intravenous atropine sulfate 0.5 mg was given. Paracetamol 1 gm was injected intraoperatively and continued every 8 h postoperatively. Before finishing the procedure by 5 min NTG infusion was discontinued to increase blood pressure. When the surgery was completed, isoflurane inhalation was discontinued, ventilation continued with pure O_2, the effect of atracurium was antagonized by intravenous neostigmine 50 µg/kg with atropine 0.01 mg/kg and the patient was extubated. Then patients stayed in the postanaesthesia care unit (PACU) for at least 1 h until complete recovery. Pain was evaluated by visual analogue scale (VAS) and patients were given increments of 2 mg morphine as rescue analgesia when VAS was >3 (with a maximum of 10 mg in 12 h postoperatively). Any side effects were recorded and managed as necessary.

Primary outcome: After finishing the surgery, the overall dose of NTG used/patient was recorded in mg.

Secondary outcome:

- After finishing the surgery the surgeon used Average category scale (ACS) [6] to grade the surgical field quality. ACS
- 1) Grade 0: No bleeding
  2) Grade 1: Slight bleeding-no blood suctioning required.
  3) Grade 2: Slight bleeding-occasional suctioning required.
  4) Grade 3: Slight bleeding-frequent suctioning required. Operative field is visible for some seconds after evacuation.
  5) Grade 4: Moderate bleeding-repeated suctioning needed. Operative field is only visible immediately after evacuation.
  6) Grade 5: Severe bleeding-continual suctioning needed. Bleeding occurs quicker than can be cleared away by suction. Surgery is hardly possible, and sometimes impossible.
- VAS for pain (ranging from 0-10 where 0 no pain and 10 maximum pain) was recorded at 30th min and the 1st, 2nd, 4th, 8th, and 12th h postoperatively.
- Duration of postoperative analgesia (the time from recovery to the first given dose of morphine), the overall dose of morphine (rescue analgesia) used, and number of patients needed analgesia were also observed.

Sample size calculation

Our pilot study showed that the overall dose of nitroglycerine required to reduce MAP to 50-60 mmhg in the same group of patients undergoing FESS under the same condition was 9 mg/patient ± 1.48. Based on the previous data and assuming an alph error of 0.05 and power of 80% (beta error of 0.2) the minimal sample size was 35 patients/group. We aimed to study 40 patients/group.

Statistical analysis

Statistical analysis was accomplished using Statistical Program for Social Science (SPSS) version 20 (IBM, Armonk, NY, USA). Data were expressed as mean ± standard deviation (SD), range, frequency, or frequency and percentage. Independent sample T test was used to analyze quantitative data. Chi-Square (X^2) test was used to analyze qualitative data. A P<0.05 was regarded to be statistically significant.

Results

Eighty patients prepared for FESS joined the study (40/Group), no patient was excluded (Figure 1). Regarding demographic data, duration of surgery, and ASA physical status, both groups were comparable (P>0.05) (Table 1). The overall dose of NTG used/patient was significantly lower in group (P) than in group (C) (5.28 ± 2.24 mg, versus 8.83 ± 1.55 mg) (P=0.001) (Table 2). The surgical field quality was better in group (P) than group (C) as ACS was significantly lower in group (P) compared to group (C) (P=0.03) (Table 3).

		Group (C)	Group (P)	p. value
Age (years)	Range	18-50	24-50	0.219
	Mean ± S. D	36.50 ± 9.43	38.80 ± 6.97	
Body weight (kg)	Range	60-84	60-83	0.513
	Mean ± S. D	72.23 ± 6.37	71.23 ± 7.22	
Sex	Male	22 (55%)	24 (60%)	0.651
	Female	18 (45%)	16 (40%)	
ASA	I	29 (72.5%)	30 (75%)	0.799
	II	11 (27.5%)	10 (25%)	
Duration of surgery (min)	Range	60-90	60-90	0.791
	Mean ± S. D	72.90 ± 8.52	73.43 ± 9.12	

Table 1: Demographic and operative data.

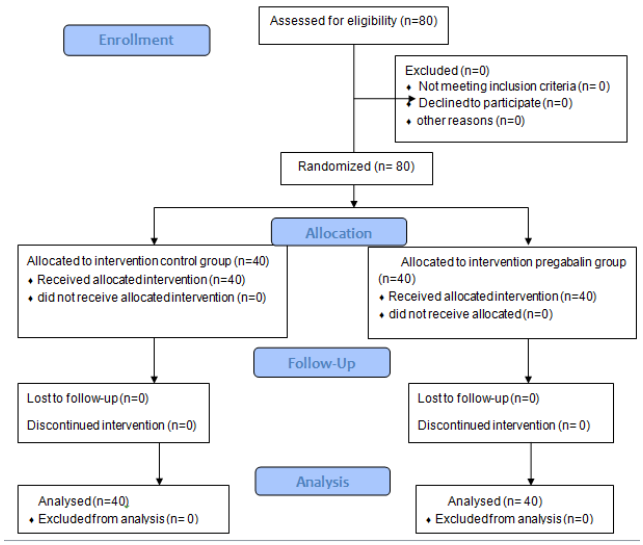

Figure 1: CONSORT Flow Diagram.

		Range	Mean ± SD	p. value
Overall dose of nitroglycerin used/ patient (mg)	Group (C)	6-13	8.83 ± 1.55	0.001*
	Group (P)	2-10	5.28 ± 2.24	

*significant difference between groups P<0.05

Table 2: Overall dose of nitroglycerin used/patient (mg).

			Group (C)	Group (P)	p. value
Average Category Scale (ACS)	0	N	1	5	0.031*
		%	2.5%	12.5%	
	1	N	12	22	
		%	30.0%	55.0%	
	2	N	20	10	
		%	50.0%	25.0%	
	3	N	4	2	
		%	10.0%	5.0%	
	4	N	3	1	
		%	7.5%	2.5%	
	5	N	0	0	
		%	0%	0%	

*significant difference between groups P<0.05; N=number

Table 3: Quality of surgical field using Average Category Scale (ACS) (0-5).

VAS		Range	Mean ± SD	p. value
30 min postoperatively	G c	0-8	5.18 ± 2.22	0.001*
	G p	0-6	3.58 ± 1.50	
1 h postoperatively	G c	0-4	2.43 ± 1.28	0.463
	G p	0-4	2.23 ± 1.14	
2 h postoperatively	G c	0-5	2.38 ± 1.44	0.001*
	G p	0-2	1.33 ± 0.69	
4 h postoperatively	G c	0-6	2.85 ± 1.73	0.002*
	G p	0-3	1.85 ± 0.89	
8 h postoperatively	G c	0-3	1.43 ± 0.84	0.413
	G p	0-3	1.28 ± 0.78	
12 h postoperatively	G c	0-3	1.48 ± 0.85	0.483
	G p	0-3	1.35 ± 0.74	

*significant difference between groups P<0.05

Table 4: Visual Analogue Scale (VAS) for pain.

Pain score (VAS) was significantly lower in group (P) compared to group (C) at 30 min, 2 h, and 4 h postoperatively but both groups were comparable regarding VAS at 1 h, 8 h, and 12 h postoperatively (Table 4). The overall dose of morphine consumed was lower in group (P) than in group (C) (2.2 ± 2.2 mg versus 4 ± 2.26 mg respectively, P=0.001) (Table 5).

Duration of postoperative analgesia was longer in group (P) than in group (C) (26.13 ± 24.22 min versus 16.33 ± 9.4 min respectively, P=0.02) (Table 5). Number of patients needed analgesia was lower in group (P) than in group (C) (22 patients versus 32 patients, P=0.017) (Table 5). As regard side effects both groups were comparable and no serious complications were detected (one patient in each group suffered from vomiting and was treated with intravenous ondansetron 4 mg).

		Group (C)	Group (P)	P
The overall dose of morphine (mg)	Range	0-8	0-6	0.001*
	Mean ± S. D	4.00 ± 2.26	2.20 ± 2.21	
Time of postoperative analgesia (min)	Range	0-30	0-55	0.020*
	Mean ± S. D	16.33 ± 9.44	26.13 ± 24.22	
Number of patients need analgesia	No	8 (20%)	18 (45%)	0.017*
	Yes	32 (80%)	22 (55%)	

*significant difference between groups P<0.05

Table 5: Postoperative data.

Discussion

Patients with sinonasal disease who did not recover by medical treatment will undergo FESS where high definition endoscope goes through the nose into the sinus. Surgery including the mucosa of the

nose leads to hypertension and tachycardia due to sympathetic stimulation. Visualization of the surgical site by endoscope will be very difficult if there is bleeding [7]. Surgical site quality during FESS can be enhanced by controlled hypotension which decreases bleeding [8].

Patients often had early pain after FESS which is aggravated by the existence of nasal tampons [9-11]. Neuropathic pain is one component of postoperative pain [12]. There are different methods to restrain postoperative pain but all these methods may be not enough for many patients [13]. Many studies showed that pregabalin (when given preoperatively) plays a remarkable role to restrain postoperative pain [14].

To our knowledge our research is the first one which estimate the influence of pregabalin (when used preoperatively) on deliberate hypotension and surgical site quality during FESS and its analgesic effect after surgery.

Our result showed that the overall dose of NTG infused, ACS, VAS for pain (30 min, 1 h, and 4 h postoperatively), morphine requirements after surgery, and number of patients requesting analgesia after surgery were significantly less in group (P) than in group (C) which showed shorter duration of postoperative analgesia.The mechanism by which pregabalin facilitates intraoperative hypotension and postoperative analgesia is not clear, but it may be interpreted by the inhibitory effect of gabapentinoids on membrane voltage dependent calcium channels. This will reduce the influx of calcium inside the cells and decrease the release of neurotransmitters (as catecholamine, glutamate, and substance P) [15,16].

Our results were supported by Mahmoud et al. [17] who used gabapentin (which belong to the same group of drug of pregabalin) preoperatively during FESS and observed that gabapentin reduced the dose of hypotensive agent used during surgery and potentiated intraoperative hypotension which resulted in reduction of the volume of blood loss during FESS. They also reported that gabapentin group was correlated with less vomiting after surgery but our study showed same incidence of vomiting in the studied groups.

Our results were supported by the results recorded by Misra S, et al. [18] who compared the influence of gabapentin when given 2 h before surgery (plus saline infiltration during surgery) and with placebo (plus lidocaine infiltration during surgery) on the hemodynamic reaction to intubation and pin insertion in the skull during elective craniotomy and observed that gabapentin abolished the increase in MAP and HR in response to pin insertion.

Our results were in line with the result recorded by Mathiesen O, et al. [19] who reported that pregabalin (300 mg preoperatively) reduced pain and analgesic requirements after tonsillectomy operation.

Our results were supported also by Jokela et al. [20] who compared preoperative single oral dose of pregabalin 150 mg or 75 mg with diazepam 5 mg in females prepared for gynecological laparoscopic surgery and found that pregabalin 150 mg was associated with lower VAS for early pain after surgery.

Also Agarwal et al. [21] used pregabalin 150 mg 1 h before laparoscopic cholecystectomy and reported that pregabalin decreased postoperative pain score and fentanyl consumption. Balaban et al. [22] used two different doses of pregabalin (150 mg and 300 mg) 1 h before laparoscopic cholecystectomy and observed that pregabalin was correlated with less pain and fentanyl consumption after surgery in comparison with placebo. Also the effect of pregabalin was dose dependent (300 mg had better analgesia and better opioid sparing effect than 150 mg).

Menda F, et al. [23] used single gabapentin dose in middle aged patients underwent cardiac surgery and reported that gabapentin decrease pain and reduce morphine requirement after surgery. In contrast to our result Chang SH, et al. [24] observed that 300 mg pregabalin preoperative didn't reduce postoperative pain and the incidence of sedation was high in the early postoperative period.

Also in contrast to our results White PF, et al. [25] used pregabalin (in dose ranging from 75 to 300 mg) as premedication for patients prepared for elective surgery in comparison to placebo and reported that pregabalin increased sedation but it did not decrease postoperative pain.

Also in contrast to our results Mathiesen O, et al. [26] reported that pregabalin when used together with paracetamol or paracetamol and dexamethasone was not associated with reduced pain score or opioid consumption after abdominal hysterectomy. The difference between our results and other results may be due to differences in doses of pregabalin, type of surgery, or methodology.

Limitations

We did not compare different doses of pregabalin to get the exact dose which gives the maximum effect and the least side effects but this may be a point for further investigation.

Conclusion

Preoperative oral pregabalin improved the quality of the surgical site during FESS, decreased the required dose of intraoperative hypotensive agent and postoperative morphine, increased the duration of postoperative analgesia, reduced VAS for pain (30 min, 1 h and 4 h postoperatively) and decreased the number of patients requesting postoperative analgesia.

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