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1 **Hypnotic technique and communication reduce pain and anxiety in peripheral**
2 **intravenous cannulation: KTHYPE, a multicentre randomised trial**

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22 **Key words:** anaesthesia, anxiety, peripheral intravenous cannulation, hypnosis, pain, patient
23 experience

24
25 Results of this study were presented at the annual meeting of the European Society of
26 Anaesthesiology in Copenhagen (June 2018) and at the annual meeting of the French Society of
27 Anesthesia and Intensive Care in Paris (September 2018).

28 **Editor's key points**

29 Use of positive words can improve pain perception and subjective patient experience.

30 The KTHYPE trial is arandomised, parallel, ~~single simple~~-blind, multicentre study comparing
31 the effects of three types of communication on pain, comfort and anxiety in preoperative
32 patients during peripheral intravenous cannulation (PIVC).

33 Pain and anxiety were decreased and comfort perception increased after PIVC when positive
34 communication and hypnosis were used.

35 This well-designed randomised controlled trial showed a significant benefit of hypnotic
36 technique during a routine perioperative procedure.

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40

41 **ABSTRACT**

42 **Background:** Clinicians traditionally warn patients of pain before peripheral intravenous
43 cannulation (PIVC). However, using words related to pain or undesirable experiences can
44 result in greater pain and anxiety. Use of positive words can improve pain perception and
45 subjective patient experience. We aimed to compare the effects of three types of
46 communication, including hypnotic communication, on pain, comfort and anxiety in patients
47 during PIVC.

48 **Methods:** The KTHYPE trial is a randomised, parallel, **single** blind, multicentre study of
49 patients undergoing PIVC on the dorsal face of the hand before surgery. Patients from three
50 hospitals were randomly allocated to one of three groups: PIVC performed with hypnotic
51 technique (hypnosis group), negative connotation (nocebo group) or neutral connotation
52 (neutral group). The primary outcome measure was the occurrence of pain measured with a
53 0 to 10 numerical rating scale just after PIVC.

54 **Results:** Of the 272 subjects analysed (hypnosis n = 89; nocebo n = 92; neutral n = 91), pain
55 after PIVC was lower in the hypnosis group (mean [SD], range) (1.5 [1.9], 0-5) compared
56 with the neutral (3.5 [2.3], 0-9 ; p < 0.0001) and nocebo groups (3.8 [2.5], 0-10 ; p < 0.0001).
57 While anxiety was higher and comfort lower before PIVC in the hypnosis group, anxiety
58 decreased and comfort perception increased after PIVC when hypnosis was used.

59 **Conclusion:** This is one of the first well-designed randomised controlled trials showing a
60 significant benefit of hypnotic technique during a routine procedure such as PIVC. The
61 results could facilitate implementation of hypnosis in daily clinical care.

62

63 **Trial registration:** [clinicaltrials.gov NCT02662322](https://clinicaltrials.gov/ct2/show/study/NCT02662322)

64 Communication is decisive in creating a therapeutic alliance with the patient. Unfortunately, a
65 routine procedure as frequent and simple as peripheral intravenous cannulation (PIVC) can
66 be a source of stress and pain. Pharmacological interventions have been shown to reduce
67 the pain associated with PIVC. A network metaanalysis suggested that PIVC pain can be
68 reduced by local anaesthesia¹. However, local anaesthesia for cannulation is usually only
69 offered to children, and fewer than half of clinicians follow this procedure for adults,^{2,3} which
70 is time-consuming³ and has a high rate of puncture failure^{2,4}. Psychological interventions
71 have also been shown to reduce the pain and anxiety associated with PIVC in children^{5,6,7}.

72 Communication skills is recognized as a key element of care,⁸ but unfortunately, clinicians
73 often warn adult patients of pain using words with a negative connotation (i.e. “painful”,
74 “sting”). This attitude is thought to be helpful and empathic. However, warning using
75 language that refers to negative experiences is associated with a modification of pain and
76 comfort perception^{9,10}. Warning the patient that the act will be painful leads to more pain and
77 anxiety and can create a nocebo effect⁹⁻¹³. On the contrary, use of positive words and
78 sentences can benefit patient comfort^{14,15}. Hypnotic communication uses positive
79 suggestions and distractions to reduce the sensitive and affective dimensions of the pain
80 experience. Hypnosis is a state of consciousness involving focused attention and reduced
81 peripheral awareness characterized by an enhanced capacity for response to suggestion¹⁶.

82 Indirect hypnosis or Ericksonian hypnosis is a method utilizing body language, conversation,
83 metaphors and other hypnotic techniques to induce therapeutic behavioural change by
84 indirect suggestion. It starts from the beginning of the relationship between therapist and
85 patient. This therapeutic alliance is essential. The **hypnotic** confusion technique uses
86 distraction to focus patients on an incongruous, unexpected element outside of their
87 preoccupation of the moment. By distracting the conscious mind, the therapist is able to open
88 the unconscious mind to hypnotic language and to take advantage of its induced
89 suggestibility to deliver an indirect suggestion of comfort. A benefit of hypnosis has been
90 shown for anxiety and pain¹⁷⁻²⁰, but only few methodologically rigorous studies applying
91 minimally effective control conditions have been published^{17,21}. We therefore assessed the

92 effects of hypnosis using positive words associated with a confusion technique on the
93 subjective experience of PIVC when compared with a placebo and neutral communication.

94

95 **METHODS**

96

97 **Study design and Population**

98 The KTHYPE study is a randomized, controlled, parallel-group, **single** blind, multicentre,
99 international clinical trial conducted in three hospitals: Rennes University Hospital (Rennes,
100 France), Saint-Gregoire Private Hospital (Saint Grégoire, France) and Cliniques
101 universitaires Saint-Luc, Université Catholique de Louvain (Brussels, Belgium). The Rennes
102 University Hospital Institutional Reviewed Board reviewed and approved this clinical
103 investigation (N°ID-RCB 2015-A01353-46), which was registered at clinicaltrials.gov
104 (NCT02662322). The study was approved by all local ethics committees (N°2015-A01353-46
105 — 2016 01 07).

106

107 Adult patients > 18 yr of age requiring a 20 G PIVC on the dorsal surface of the hand before
108 a scheduled surgery were included. Non-inclusion criteria were: unable to communicate in
109 French, history of difficult venous access, premedication, pregnant or breast-feeding women,
110 legally protected (under judicial protection, guardianship or supervision, persons deprived of
111 their liberty) and urgent surgery. In case of failure during the first attempt of PIVC, the patient
112 would be excluded from the study. All eligible patients gave their written consent prior study
113 participation.

114

115 **Procedure**

116 An information sheet about the study was given to all patients during the preoperative
117 consultation. After arriving in the operating room, eligible patients were informed of the study
118 by an anaesthesiologist not involved in the care of the patient and called an
119 “anaesthesiologist researcher”. He/she was blind to the allocation group and proposed to the

120 patient to participate as follows: “*A peripheral intravenous cannulation is necessary for your*
121 *anaesthesia. We currently investigate how different procedures are perceived during the*
122 *venous cannulation process. If you accept to participate in this trial, we will ask you to*
123 *evaluate your experience during venous cannulation.*”

124

125 Subjects were randomised in three groups (hypnosis, placebo or neutral) using a computer-
126 generated randomization table stratified by investigation site with a 1:1:1 ratio. Subjects were
127 blind of the allocation group. The primary evaluation criterion was assessed by the patient
128 him/herself (self-evaluation). The anaesthesiologist researcher assessed the presence of
129 movements and/or vocalization during PIVC. During the study period, subjects and
130 anaesthesiologist researchers were kept blind to the randomization group. The
131 anaesthesiologist and the anaesthesiologist nurse both called clinicians in the study were
132 different from the anaesthesiologist researcher and were not blinded. They did not participate
133 in the assessment of subjects at any time.

134 In all groups, clinician’s experience for PIVC was at least three years. No local anaesthesia
135 was allowed before PIVC. Only one attempt was allowed and the clinician catheterizing was
136 the only one talking to the patient at the time. In the hypnosis group, clinicians were
137 anaesthesiologists or nurses with a diploma in therapeutic and hypnotic communication and
138 a minimum of one year of experience. In the placebo and neutral groups, clinicians were
139 anaesthesiologists or nurses with no training in therapeutic communication and / or hypnosis.
140 During the procedure, clinicians communicated with the patient in a structured and
141 standardized way depending on the allocation group (Table 1). In the hypnosis group,
142 clinicians applied classical non-verbal hypnotic tools adapted to the subject and indirect
143 suggestion of comfort by body language. The whole procedure lasted < 5 min.

144

145 **Outcomes**

146 The primary outcome was occurrence of pain just after PIVC assessed using a numerical
147 rating scale (NRS) ²². Secondary outcomes were perception of comfort and anxiety before

148 and after PIVC measured with a validated NRS ^{23 24}. Pain, comfort and anxiety were self-
149 evaluated by subjects minutes before and after PIVC. Subjects evaluated themselves before
150 seeing any needle.

151

152 **Data Collection**

153 At each participating centre, data were collected and entered into the electronic web-based
154 case report form (eCRF) by two investigators (NF, FR) blinded to the allocation group, under
155 the supervision of the trial site investigators. Data collection was monitored by trained clinical
156 research associates.

157 Data collected by the anaesthesiologist researcher were anthropometric (age, gender and
158 body mass index), type of surgical procedures according to the classification of the American
159 Heart Association (ACC/AHA)²⁵, standard of education and socio-economic category. In
160 order to ensure blinded evaluation, the presence or not of spontaneous patient arm, face
161 withdrawal, smile and/or an unprompted vocalization or comments were also recorded by the
162 anaesthesiologist researcher.

163 Subjects were asked to quantify their pain, anxiety and comfort on 11-point NRS (0 = no pain
164 – 10 worst imaginable pain experience, 0 = no anxiety – 10 = worst imaginable anxiety and 0
165 = no comfort – 10 = best imaginable comfort) just before (for anxiety and comfort only) and
166 within 3 min after the completed peripheral intravenous cannulation.

167

168 **Statistical analysis**

169 Based on an expected mean (SD) NRS value of 4.4 (2.4) in the nocebo ¹³, We included 88
170 subjects in each group to show a decrease in NRS of 15% in the neutral group and 30% in
171 the hypnosis group (effect size of 0.05), assuming an alpha risk of 5% and a power of 90% in
172 a two-sided one-way analysis of variance (nQuery 8, V.8.3.1.0, Cork, Ireland). Based on the
173 Gupta and colleagues who calculated sample size with a hypothesized 20% decrease in
174 NRS ¹³, we considered that a 30% decrease in NRS would reflect a clinically relevant effect
175 and that 15% would indicate a significant but less clinically relevant effect in the neutral

176 group as compared with placebo. We included 10% more subjects to take into account
177 expected cases of failure of the first attempt of PIVC, or 300 subjects to obtain a minimum of
178 264 included.

179 Statistical analysis was performed with SAS V9.4 (SAS Institute, Cary, NC, US). All data
180 analyses were performed by researchers blinded to group allocation. Normal distribution was
181 assessed by descriptive statistics and histograms. Quantitative variables are presented as
182 mean (SD) for continuous variables and as number (%) for categorical variables. Analysis of
183 study outcomes was performed by one-way analysis of variance for continuous variables and
184 chi-square test or Fisher exact test for categorical variables. In cases of statistical
185 significance, two-by-two comparisons were performed with a Bonferroni adjustment threshold
186 for multiple testing. A sensitivity analysis taking into account the standard of education was
187 also performed for the primary outcome using two-way analysis of variance in which the
188 group:standard of education interaction was tested.

189

190 **RESULTS**

191 Between March 2016 and March 2017, a total of 294 patients were randomised (Figure 1)
192 from Rennes hospital: 62 recruited / 50 analysed; St Gregoire Hospital: 132 recruited / 128
193 analysed and St Luc Hospital: 100 recruited / 94 analysed. First attempt cannulation failure
194 was 6.5% leaving 272 subjects analysed (Hypnosis group n = 89; Neutral group n = 92;
195 Nocebo group n = 91). Subject characteristics are presented Table 2. Study groups were
196 similar in gender, body mass index, types of surgical procedures, standard of education
197 or socio-economic category. Self-evaluation of pain, anxiety and comfort was performed
198 within 3 min after the end of PIVC (2.5 [2.8] min) without differences between groups.

199

200 The primary outcome, pain after PIVC, was significantly lower in hypnosis group compared
201 with the neutral and placebo groups (Figure 2). This difference in pain after PIVC was still

202 significant after adjustment for standard of education. There was no significant difference in
203 pain after PIVC between neutral and placebo groups.

204 Subjects in the hypnosis group were less likely to spontaneously withdraw their arm or face
205 ($n = 1$ (2%)) \ compared with the neutral group ($n = 17$ (31.5%)) or placebo group ($n = 15$
206 (22.4%)) ($p < 0.05$ for both comparisons without difference between neutral and placebo
207 groups ($p = 0.78$)). Negative face (grimace in pain) was higher in the placebo group ($n = 32$
208 (47.8%), $p < 0.01$) and neutral group ($n = 27$ (50%), $p < 0.01$) compared with the hypnosis
209 group ($n = 9$ (18%)). Positive face (smile) was higher in the hypnosis group ($n = 31$ (62%)
210 compared with the placebo ($n = 2$ (3%), $p < 0.0001$) and neutral groups ($n = 1$ (2%), $p <$
211 0.0001). No difference between groups was observed for unprompted vocalization or
212 comments.

213 Anxiety before PIVC was higher in the hypnosis group compared with the neutral group but
214 not with the placebo group (Table 3). Comfort before PIVC was lower in the hypnosis group
215 compared with the neutral and placebo groups. Anxiety after PIVC decreased in the hypnosis
216 group but not in the placebo and neutral groups. Comfort increased after PIVC in the
217 hypnosis group and decreased in the neutral and placebo groups. When anxiety and comfort
218 after PIVC were adjusted to those before PIVC, anxiety after PIVC was significantly lower
219 and comfort significantly higher in the hypnosis group compared with the neutral and placebo
220 groups (Figure 3). No differences were observed between neutral and placebo groups.

221

222 **DISCUSSION**

223

224 To our knowledge, this is the first randomised controlled trial showing the benefit of hypnosis
225 on a routine procedure as simple as PIVC. Pain and anxiety decreased and comfort
226 perception increased after PIVC when hypnosis was used. Previous studies reported pain scores
227 after 20 G PIVC placed on the dorsal surface of the hand similar to values observed in our control groups
228 (neutral/placebo)²⁶⁻²⁸. The levels of pain NRS obtained with hypnotic communication in our study were similar to
229 those reported with local anaesthesia²⁶⁻²⁸. Therefore, hypnosis with confusion technique seems to offer a benefit

230 comparable to **invasive** pharmacological-interventions. Moreover, this benefit was not associated with side effects
231 and was not time-consuming (< 3 min). Our first attempt failure rate (6.5%) was lower than in previous studies (7-
232 16%)^{29 30}. The low rate of failure in our study could be explained by the lack of local anaesthesia, which can
233 increase puncture failure,^{28 30} and by the experience of the staff in our study. Our results also show that a
234 **hypnotic** confusion technique could be applied without impacting the efficiency of PIVC. A previous study showed
235 the influence of negative words on pain during blood sampling³¹. However, physicians involved in that study were
236 not trained in hypnotic communication. The non-verbal part of the experience was then missing. In our study, only
237 the verbal language could be standardized. Our therapists adapted complex non-verbal communication to each
238 subject and indirect suggestions were induced from the outset with the therapeutic alliance.

239

240 Dutt-Gupta and colleagues¹³ showed that warning patients of a 'sting' before PIVC may not
241 be helpful. Comparing communication with positive or negative words, they reported no
242 differences in pain and Likert scale scores. However, they reported (as a secondary
243 outcome) less patients vocalizing pain during PIVC with positive communication. In our
244 study, hypnotic communication produced decreased pain perception not only compared with
245 the nocebo group but also with the neutral group. As the hypnotic process can play a crucial
246 role in the modulation and perception of pain, our results show that use of positive words
247 involving hypnotic communication could also reduce anxiety and improve comfort.
248 Furthermore, pain perception, anxiety, and comfort were similar in the neutral and nocebo
249 groups suggesting that a neutral attitude is as deleterious as a nocebo one. Our findings
250 confirm that warning patients with nocebo and even neutral words, although made with good
251 intent, induced discomfort. Hypnosis can be defined as an altered conscious state of focused
252 attention that involves absorption, some dissociative elements, and an increased
253 responsiveness to suggestion. In other words, the hypnotic cerebral process is well known to
254 improve suggestibility. The verbal distraction and focalization included in the **hypnotic**
255 confusion technique by saying something like "is your bike still going to the pool?" just before
256 PIVC created confusion in patient's mind. The patient may ask "what did he/she say?" and at
257 this time the patient is "dissociated" and focused on the meaning of the sentence rather than
258 on the PIVC.

259

260 Overall patient satisfaction is correlated with communication and pain management ³² and
261 can be improved with hypnosis³³ . In the perioperative setting, PIVC is one of the major
262 sources of preoperative anxiety³⁴. Comfort obtained by hypnotic communication before
263 surgery may help improve patient satisfaction¹⁷. Hypnotic communication, or at least
264 therapeutic communication, should be mandatory in the initial training of caregivers.

265

266 One limitation is that the study was single blinded. We chose to perform PIVC in the hypnotic
267 group by **non-blinded** anaesthesiologists and nurses with a hypnotic communication diploma.
268 We hypothesized that hypnotic communication would have too much influence on non-verbal
269 communication to not impact the relation with patients. If clinicians with a hypnotic
270 communication diploma are able to suggest comfort, they could also suggest pain and
271 discomfort if they performed PIVC for neutral and nocebo groups. **Another limitation is the**
272 **restriction of the hypnotic group to anaesthesia providers with a hypnotic communication**
273 **diploma. Whether the salutary effects of hypnosis are the same when providers not trained in**
274 **hypnosis use the same technique needs further research.**

275

276 Our study did not show the benefit of the **hypnotic** confusion technique *per se* as it was
277 provided by clinicians with a hypnotic communication diploma. We cannot conclude that the
278 **hypnotic** confusion technique provided by clinicians without a diploma would have any
279 benefit. Indeed, Lang and colleagues ³⁵ showed that hypnosis compared to attentive
280 behaviour alone provides greater effects on pain and anxiety reduction during invasive
281 medical procedures. Thus hypnotic communication involving a confusion technique may be
282 more efficient than distraction alone to reduce pain and anxiety during PIVC. Further studies
283 are necessary to test this hypothesis. Finally, anxiety was more important in the hypnosis
284 group before PIVC compared with other groups. These differences happened despite
285 randomization. However, subjects in the hypnosis group were less anxious and more
286 comfortable after PIVC, which is what matters because it is what they will remember. When

287 patients are in a comfortable state, they are likely to stay in that state and uncontrollable
288 anxiety is prevented³⁶. In other words, a good experience with PIVC can determine the
289 quality of the subsequent experience in the hospital.

290

291 In conclusion, the KTHYPE trial is the first randomised, multicentre study evaluating the
292 effect of communication on pain, comfort and anxiety in surgical patients undergoing PIVC. It
293 shows that hypnotic communication with a confusion technique compared to neutral or
294 placebo communication decreases pain and anxiety after PIVC. These results suggest that
295 implementation of hypnosis into daily care and could lead to significant changes in the
296 standard of care in anaesthesia.

297 **Authors' contributions**

298 NF, FB, FR, CW, HM, BL and HB contributed to the conception and design of the research
299 protocol. NF was the principal investigator. He included patients in his centre and wrote the
300 first draft of the manuscript. HB provided critical input in the writing of the manuscript. BL
301 provided critical input for the methodology. NF, FB, FR, CW and HM included patients in their
302 centres and critically revised and modified the manuscript. BL was responsible for the
303 statistical analysis. All authors approved the final version of the manuscript.

304

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308 the collection, management, analysis, and interpretation of the data; or the preparation,
309 review, or approval of the manuscript.

310

311 **Declarations of interest**

312 The authors have no relevant conflicts of interest.

313

314

315 **Legends of the figures**

316

317 **Figure 1.** KTHYPE study flow chart.

318

319 **Figure 2.** Self-evaluated pain after peripheral intravenous cannulation (PIVC) on an 11-point
320 Numerical Rating Scale (NRS) (0 = no pain – 10 worst imaginable pain experience) for
321 Hypnosis (n=89), Neutral (n=92) and Nocebo (n=91) groups. Median, first quartile and third

322 quartile are represented by box. Whisker plots represented 1.5 interquartile space associated
323 with outliers for Hypnosis group. Mean is represented by rhomb. *** $p < 0.0001$. NS = not
324 significant.

325

326 **Figure 3.** Self-evaluated anxiety and comfort after peripheral intravenous cannulation (PIVC)
327 on an 11-point Numerical Rating Scale (NRS) for Hypnosis (n=89), Neutral (n=92) and
328 Nocebo groups (n=91). Median, first quartile and third quartile are represented by box. Mean
329 is represented by rhomb. Whisker plots represented 1.5 interquartile range associated with
330 outliers. *** $p < 0.0001$. NS = not significant.

331

332

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Figure 1

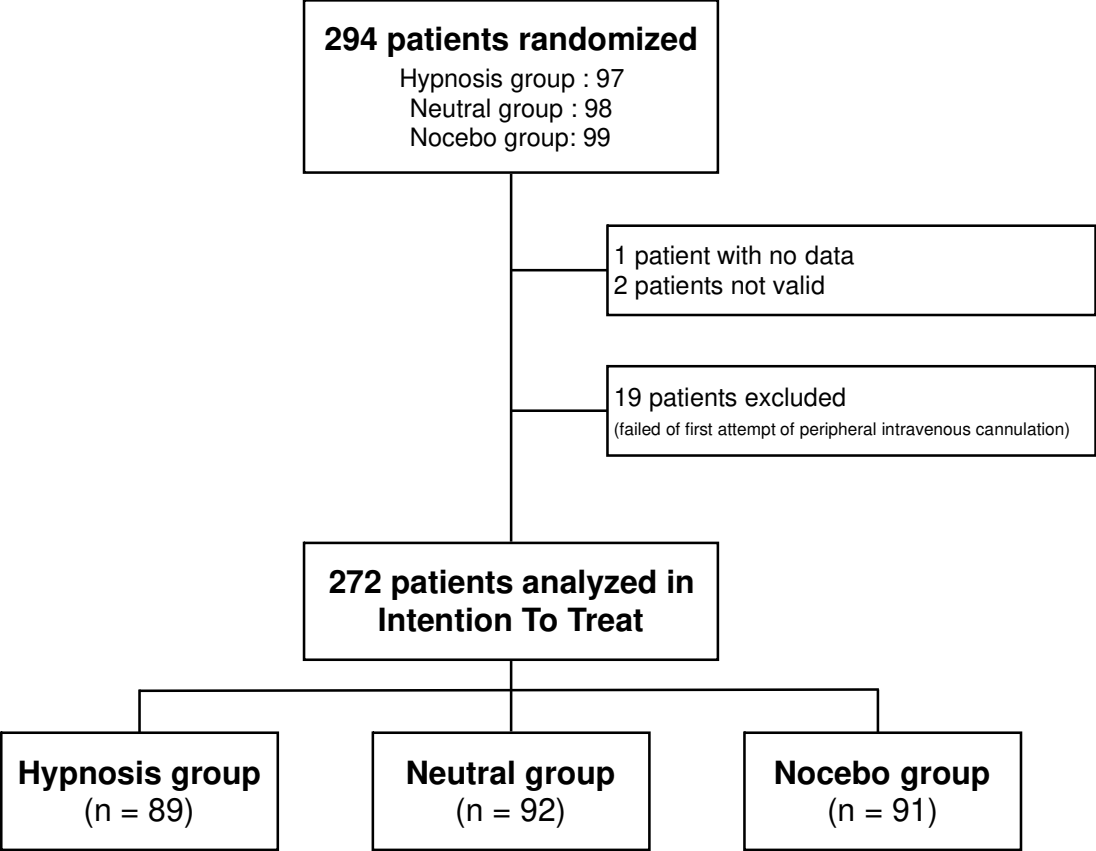


Figure 2

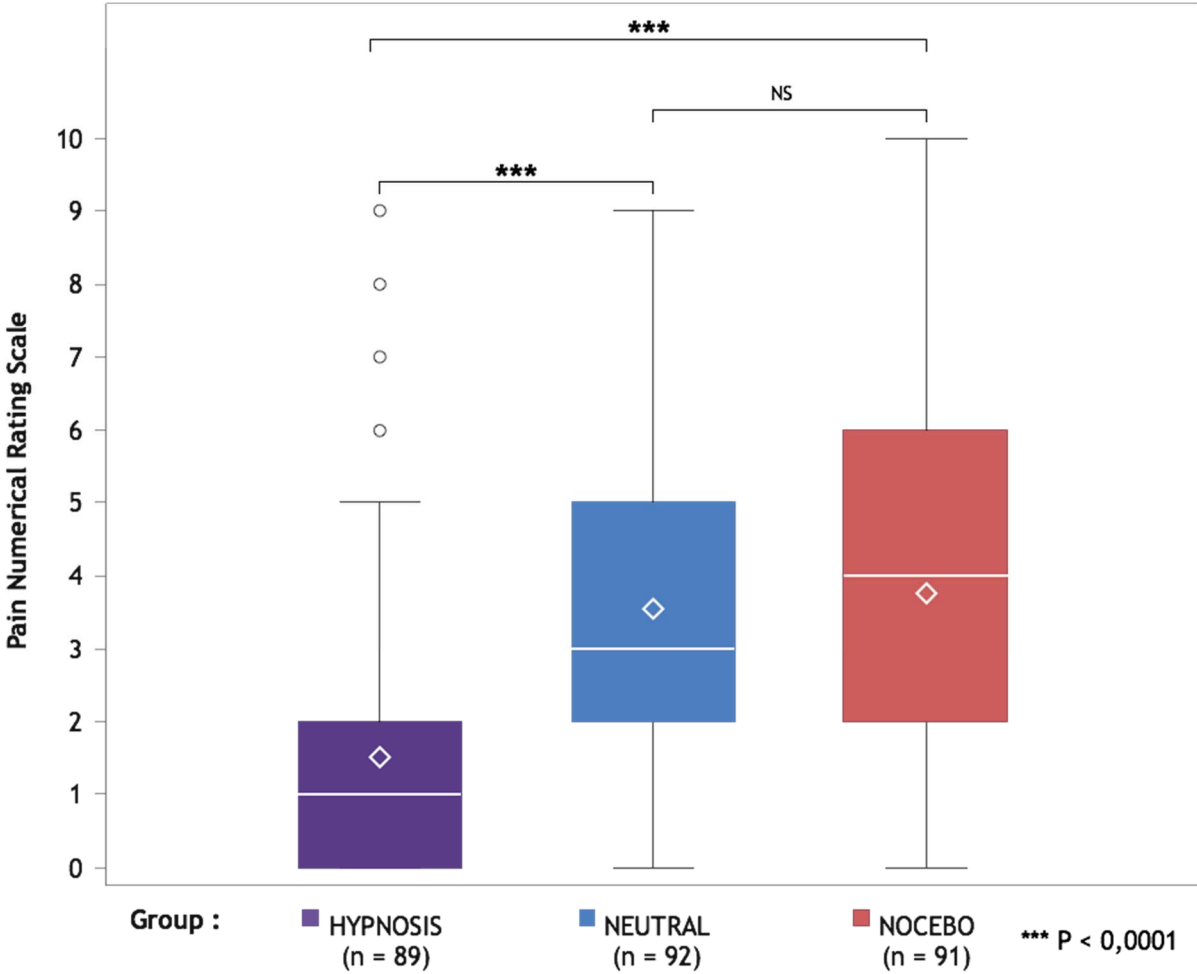


Figure 3

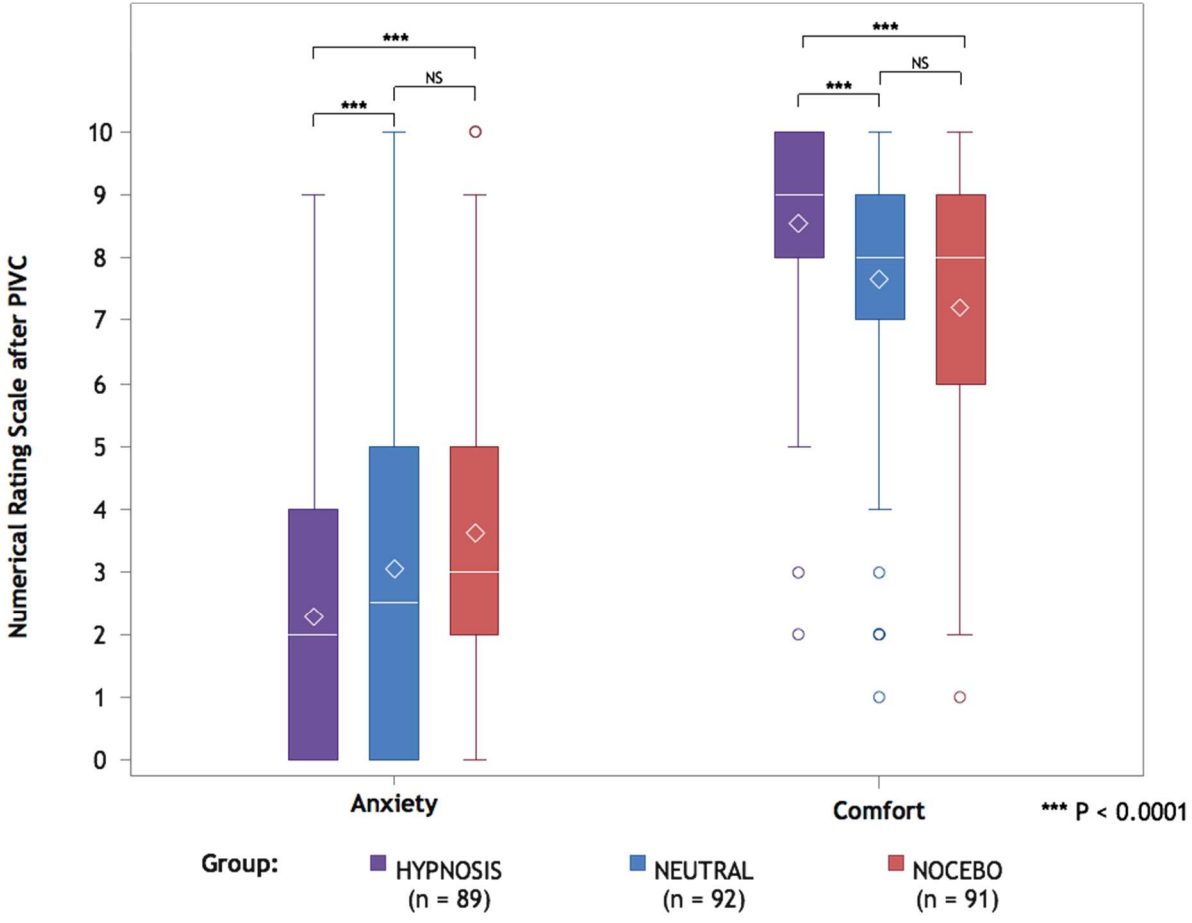


Table 1

Structured and standardized communication during peripheral intravenous cannulation.

	Placing tourniquet around the arm	Decontaminating skin with light friction	Inserting peripheral intravenous catheter
Hypnosis	"How did you come to the hospital?"	"How long did it take you to come here?"	"Is your bike still going to the pool?"
Neutral	"I am placing the tourniquet to dilate the vein."	"I am decontaminating the skin."	"I am putting the catheter in."
Nocebo	"I am placing the tourniquet, it grips/squeezes hard!"	"It is cold!"	"Warning, I will sting. One, two, three, it stings!"

Table 2**Subject characteristics**

	Total (n=272)	Hypnosis (n=89)	Neutral (n=92)	Nocebo (n=91)
Demographics				
Mean age (SD) - yr	54.5 (17.5)	56.2 ± 16.9	53.7 ± 16.9	53.7 ± 18.6
Sex (F/M) - %	55 / 45	54 / 46	52 / 48	60 / 40
Mean BMI (SD) – kg m ⁻²	25.7 (5.2)	26 ± 5.9	25.1 ± 4.3	25.9 ± 5.3
Surgery Procedure Risk (ACC/AHA) - no. (%)				
High	11 (4)	8 (9)	2 (2)	1 (1)
Intermediate	81 (30)	22 (25)	27 (29)	32 (35)
Low	180 (66)	59 (66)	63 (68)	58 (64)
Standard of education - no. (%)				
No qualification	26 (10)	10 (11.4)	11 (12.0)	5 (5.5)
School (US) / Secondary School (UK)	75 (28)	24 (27.3)	29 (31.5)	22 (24.2)
High school (US) / A-Levels (UK)	60 (22)	16 (18.2)	19 (20.7)	25 (27.5)
University (US) / Higher Education (UK)	110 (41)	38 (43.2)	33 (35.9)	39 (42.9)

There were no significant differences ($p < 0.05$) between study groups. BMI, body mass index.

Table 3

Numeric Rating Scale (NRS) of anxiety and comfort self-evaluated before and after peripheral intravenous cannulation (PIVC) in Hypnosis group compared to Neutral and Nocebo groups.

	Hypnosis (n = 89)	Neutral (n = 92)	Nocebo (n = 91)
Before PIVC			
Anxiety	4.4 (2.6) [0-10] *	3.0 ± 2.6 (0-10)	3.5 ± 2.7 (0-10)
Comfort	7.5 ± 2.1 (2-10)* [§]	8.5 ± 1.6 (3-10)	8.3 ± 1.8 (3-10)
After PIVC			
Anxiety	2.3 ± 2.5 (0-9)* [§]	3.0 ± 2.9 (0-10)	3.6 ± 2.7 (0-10)
Comfort	8.5 ± 1.7 (2-10)* [§]	7.7 ± 2.2 (1-10)	7.2 ± 2.1 (1-10)
Pain	1.5 ± 1.9 (0-9)*[§]	3.5 ± 2.3 (0-9)	3.8 ± 2.5 (0-10)
Difference before and after PIVC			
Anxiety	-2.1 ± 2.9 [£]	+0.0 ± 2.3	+0.1 ± 2.3
Comfort	+1.0 ± 2.1 [£]	-0.9 ± 1.9 [£]	-1.1 ± 2.1 [£]

NRS — mean (SD) [range]. Comparison of pain, anxiety and comfort NRS after PIVC are adjusted to those before. * p<0.05 vs neutral. [§] p<0.05 vs nocebo. [£] p<0.05 before vs after