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Original Research Article

The Lack of Efficacy of Different Infusion Rates of Intrathecal Baclofen in Complex Regional Pain Syndrome: A Randomized, Double-Blind, Crossover Study

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Abstract

Objective. Intrathecal baclofen (ITB) is effective in the treatment of dystonia related to complex regional pain syndrome (CRPS). In a previous study, we noted that the responsiveness to ITB declined in 30% of patients once drug delivery was switched from an external to an implanted device associated with a reduction of the infusion rate (IR).

Design. In a double-blind study, we investigated the effect of varying the IR at a fixed daily dose on the efficacy and safety of ITB in patients with CRPS-related dystonia. Patients were randomized to either slower infusion rate delivery (SIRD) or four-times faster infusion rate delivery (FIRD) for 2 weeks and were crossed over after a 1-week washout period.

Patients. Patients were eligible if they experienced no beneficial response to ITB on dystonia despite a minimum dose of 600 μg/day, or because side effects limited dose escalation.

Outcome Measures. Primary outcome measures were changes in global dystonia and pain severity.

Results. There were no significant differences between the FIRD and the SIRD groups for the median change of numeric rating scale dystonia (–0.3 [interquartile range {IQR} –1.1–0.5]), pain (0.1 [IQR –0.8–1.3]), and secondary outcomes, except for the frequency of adverse events, which was significantly higher during FIRD (12 vs 2). FIRD was preferred only by patients who were included because side effects to ITB prevented dose escalation.

Conclusions. Increasing the IR at a fixed daily dose is not associated with improvement of dystonia or pain but warrants further investigation in patients in whom side effects prevent further dose escalation.

Key Words. Infusion; Rate; Intrathecal; Baclofen; CRPS

Introduction

Complex regional pain syndrome type I (CRPS I) is commonly preceded by injury, usually to a limb, and is characterized by pain, disturbed blood flow, temperature regulation, and motor control of the affected area [1–3]. Approximately 20% of patients with CRPS develop dystonia, which is characterized by fixed flexion postures [1,4–7]. Because dystonia in CRPS tends to spread to other limbs, the syndrome may evolve into a disabling disorder with a marked impact on quality of life [4,6,8]. Impaired inhibitory control of sensorimotor circuits is a key pathophysiological finding in dystonia of CRPS [9]. Baclofen stimulates pre- and postsynaptic gamma-aminobutyric acid B receptors, which enhances central inhibitory activity [10,11]. However, dystonia in CRPS is rarely controlled by oral baclofen, probably because of the drug's poor ability to pass the blood–brain barrier [12,13]; although in some patients, beneficial effects are reported with dosages as high as 90–120 mg/day [4]. Epidural administration of baclofen was shown to be beneficial in intractable spasticity likely because the drug is lipid soluble and may cross the dura to act on the spinal canal [14]. Intrathecal delivery of baclofen overcomes the obstacle of the blood–brain barrier and results in greater therapeutic efficacy concentrated at the spinal site of

Table 1 Drug delivery characteristics during screening procedure and post-pump implantation [16]

	Screening procedure	Postimplantation
Median (IQR) daily dose ITB (μg)	375 (275–500)	695 (393–838)
Concentration baclofen (mg/mL)	0.5	3
Median (IQR) infusion rate ITB (mL/day)	0.74 (0.54–0.98)	0.24 (0.13–0.28)

IQR = interquartile range; ITB = intrathecal baclofen.

action [15,16]. However, not all patients may respond to this mode of drug delivery, which is expensive and requires an invasive implantation procedure. Hence, a screening procedure with an external pump is frequently used to evaluate the responsiveness to intrathecal baclofen (ITB) to help select those patients that are most suitable for continuous ITB delivery through an implanted pump. Against this background, we screened patients using a 2-day placebo run-in dose escalation (200–800 μg ITB) design [16]. The responder criterion for pump implantation was set at a ≥25% improvement of global dystonia severity on two consecutive baclofen days as compared with placebo. However, after pump implantation, 30% of patients on ITB surprisingly failed to meet the responder criterion of the screening despite the use of a minimum daily dose of 600 μg or because side effects limited dose escalation. In an attempt to find an explanation for this finding, we reviewed the procedures of our study [16]. We found that the infusion rates (IRs) applied during the screening and postimplantation period differed because of the use of different baclofen concentrations (0.5 mg/mL vs 3 mg/mL) (Table 1). The IRs decreased once patients were switched to 3 mg/mL concentration in the postimplantation period. Two different concentrations were used because of the utilization of two pumps with different requirements for effective drug delivery. Could the lack of response to ITB in some patients, after the switch to the higher baclofen concentration, be explained by the use of lower IRs? In an animal model, higher IRs of baclofen and bupivacaine increased the drug's cerebrospinal fluid distribution; although experiments were performed in a nonphysiological setting [17] and pain severity was reduced by increasing the IR of intrathecally delivered bupivacaine in patients with intractable pain [18]. To our knowledge, the influence of the IR on the clinical efficacy of ITB, independent of the daily dose, has not been described to date. In this study, we compared the efficacy and safety of two ITB IRs at a fixed daily dose in patients with CRPS-related dystonia and hypothesized that the clinical efficacy may improve by increasing the IR without affecting safety as the daily dose was fixed.

Methods

Patients

The study was conducted in an ambulatory setting between April and December 2008. Patient consent was obtained in accordance with the declaration of Helsinki, and the study was approved by the local Ethics Committee. The trial was registered in The Netherlands National Trial Register (NTR 1269). All patients were followed in our outpatient clinic and had CRPS-related dystonia in at least one extremity for which continuous ITB was administered. The patients fulfilled the CRPS criteria of the International Association for the Study of Pain including continuing pain; allodynia or hyperalgesia disproportionate to any inciting event; evidence at some time of edema; changes in skin blood flow or abnormal sudomotor activity in the area of pain; and the absence of any condition that would otherwise account for the degree of pain and dysfunction [2]. Patients had received an internal programmable Synchromed EL or II® pump (Medtronic, Minneapolis, MN, USA) for continuous infusion of ITB after oral baclofen up to a minimal daily dose of 60 mg failed to provide beneficial response or side effects limited escalation of the daily dose [16]. Patients were eligible for the IR study if they experienced no beneficial response to ITB on dystonia at a minimum daily dose of 600 μg, or dose-limiting side effects prohibited dose escalation of ITB. Furthermore, patients had to rate their global dystonia severity as at least 5 on a numeric rating scale (NRS) ranging from 0 (absent) to 10 (most severe) in order to be eligible for the study. Exclusion criteria were identical to those used in a previous study examining the efficacy of ITB in CRPS-related dystonia [16]. In 11 patients, a screening procedure was performed using an external microinfusion pump before pump implantation [16]. The remaining three patients participated in a trial with intrathecal glycine, after which they were switched to ITB without a screening procedure [19]. These three patients were included in this study because they failed to improve ≥25% in dystonia severity as a result of dose-limiting side effects to ITB. Pump-catheter system integrity was verified in all patients prior to the study, and other conditions potentially influencing dystonia severity were ruled out. At baseline, the administered daily dose varied between patients, and all patients used a baclofen solution of 3 mg/mL.

Design

In a double-blind, randomized, two-period, crossover design, solutions of 3 and 0.75 mg/mL baclofen were administered in a randomized sequence. A computer method was used to randomly allocate patients to one of the two sequences of different IRs. Prior to the start of the study, all patients received ITB at a simple continuous rate with a 3 mg/mL concentration. To obtain two IRs at a 4:1

ratio with a fixed daily dose, concentrations of 3 mg/mL (slower infusion rate delivery [SIRD]) and 0.75 mg/mL (faster infusion rate delivery [FIRD]) were used. A physician who was not involved in the assessments of the patients carried out the switch procedure at the start of each sequence, filling the pump reservoir with baclofen concentrations of 0.75 or 3 mg/mL. Notably, reservoir fillings were always changed, regardless of the assigned new concentration to guarantee maintenance of blinding. When the baclofen concentration is changed, a bridge bolus can be used to empty the internal pump tubing and external catheter with the old baclofen concentration with the original IR. With a fixed daily administered dose, the replacement of the 3 mg/mL concentration will result in a substantial delay before the new concentration reaches the tip of the catheter. As this concentration-dependent delay may potentially contribute to deblinding, we used the side port to carry out a procedure that included aspiration of the content of the external catheter followed by multiple boluses to replace the removed volume. As a result of this approach, the new concentration would always reach the tip of the catheter within an hour regardless of the old concentration. During the first 2 weeks of the study, the first assigned IR was used. This was followed by a 1-week open administration of the 3 mg/mL concentration of baclofen to minimize potential consequences of any carryover effect. Subsequently, over the following 2 weeks, patients received the other IR.

Outcome Measures

Patients were asked to rate the global severity of pain and dystonia using an NRS ranging from 0 (absent) to 10 (most severe) once every day starting 1 week before the first switch procedure until the end of the second treatment period. At the start and end of each treatment period prior to changing the IR, a blinded clinical assessor rated the dystonia severity using the Burke–Fahn–Marsden (BFM) scale, which is the sum of the scores of the individual body regions [20]. The same rater assessed the change of CRPS signs and symptoms from baseline on a global impression scale (GIS) at the end of each treatment, ranging from –3 (much worse) to +3 (much better) with 0 for "no change." At the end of the study, patients were asked to compare both treatment periods using a patient preference questionnaire (PPQ). The PPQ consists of a 10-cm horizontal line ranging from –5 to +5. A score of 0 reflects no preference, whereas –5 or +5 expresses maximal preference for the first or second treatment period, respectively. In addition, patients were asked to indicate the reasons for their preference. At the end of each study the clinical assessor was asked to guess treatment assignment to evaluate the integrity of blinding. The primary outcome measure was the difference in change in global severity of pain and dystonia between baseline and end of each IR period. The secondary outcome measures were defined as the difference in change in BFM score between baseline and end of each IR period, the difference in GIS between both treatment periods, the PPQ score, and the frequency and severity of adverse events assessed at the end of each IR period.

Statistical Analysis

The results are expressed as median (interquartile range [IQR]). For all variables, a Wilcoxon signed rank test or Mann–Whitney *U* test was used to examine differences within and between patients, respectively. A chi-square test was conducted to compare the amount of adverse events between the FIRD and the SIRD groups. Significance was assumed at the 0.05 level. Assuming an alpha of 0.05, beta of 0.2, a standard deviation of the NRS of 2, and a correlation between measures of 0.6, we calculated that 14 patients would be required to detect a statistically significant difference of ≥25% in the reduction of NRS scores between both IRs.

Results

Demographic and Baseline Characteristics

Fourteen CRPS patients (13 women) aged 45.5 years (IQR 37.3–56.0) with a median disease duration of 12.5 years (IQR 8.0–16.3) were found eligible and participated in the study (Table 2). The median daily dose of ITB was 695 μg (IQR 393–838), with the median thoracic level of the catheter tip at T7 (range T2–T11). Seven patients (six women) were allocated to the FIRD–SIRD sequence; seven patients (all women) were allocated to the SIRD–FIRD sequence. All patients completed the study. A Wilcoxon signed rank test indicated there were no significant

Table 2 Demographic and clinical characteristics

Characteristics	Value
Median (IQR) age (years)	45.5 (37.3–56.0)
Sex	
Male	1
Female	13
Median (IQR) dystonia NRS	7.2 (5.9–8.0)
Median (IQR) pain NRS	6.4 (5.5–7.8)
Median (IQR) duration of CRPS (years)	12.5 (8.0–16.3)
Median (IQR) duration of dystonia (years)	12.5 (7.8–16.3)
Median (IQR) duration of ITB (years)	3.9 (2.6–5.1)
Number of affected extremities (%)	
1	0 (0)
2	1 (7)
3	2 (14)
4	11 (79)
Number of dystonic extremities (%)	
1	0 (0)
2	1 (7)
3	3 (21)
4	10 (72)
Median (IQR) Burke–Fahn–Marsden score	47 (33–62)

IQR = interquartile range; NRS = numeric rating scale; CRPS = complex regional pain syndrome; ITB = intrathecal baclofen.

Table 3 Baseline scores for primary and secondary outcome measures

Measure	FIRD, median (IQR)	SIRD, median (IQR)	*P* value
Primary outcome measures			
NRS for dystonia	7.4 (5.9–8.3)	7.4 (6.4–8.1)	NS
NRS for pain	6.7 (5.5–7.5)	7.0 (5.9–7.8)	NS
Secondary outcome measure			
Burke–Fahn–Marsden scale	50 (33–60)	48 (32–65)	NS

NS = not significant; FIRD = faster infusion rate delivery; SIRD = slower infusion rate delivery; NRS = numeric rating scale.

differences between baseline measures (NRS for dystonia and pain and BFM) of the first and second treatment period for each sequence, indicating a successful washout (Table 3). Additionally, a Mann–Whitney *U* test indicated that there were no significant differences between these baseline measures of patients assigned to each treatment sequence (FIRD–SIRD or SIRD–FIRD).

Results on Outcome Measures

There were no significant differences between the FIRD and the SIRD group in median change of NRS score for dystonia (–0.3 [IQR –1.1–0.5]) and pain (0.1 [IQR –0.8–1.3]) and BFM score (2 [IQR –4–13]) (Table 4). Six patients preferred FIRD with a median PPQ score of 3.0 (IQR 1.6–4.3), and seven patients favored the SIRD with a median PPQ score of 3.0 (IQR 1.0–3.0). One patient had no preference for any of the IRs. The difference between both groups in PPQ score was not significant. After FIRD, six patients showed an improvement on the GIS (+1 in four and +2 in two patients), three patients deteriorated (–1 in two and –2 in one patient), and five patients showed no change. After SIRD, four patients showed an improvement on the GIS (+1 in three and +3 in one patient), three patients deteriorated (–1 in one and –2 in two patients), and seven patients showed no change. There was no significant difference in change found on the GIS score between both IRs ($z = -1.66$). There was no significant effect of IR sequence on any of the outcome measures. Twelve adverse events (five moderate, seven mild) were reported in eight patients on FIRD (Table 5). Headache was the most frequently reported adverse event (N = 5), which in three patients was typical of intracranial hypotension headache and likely resulted from aspiration of catheter content during the switch procedure. Two patients reported one adverse event (both mild) while on SIRD including one patient with intracranial hypotension headache. There were significantly more adverse events on FIRD compared with SIRD ($\chi^2 = 6.78$, df = 1, $P = 0.01$), even after the removal of events due to intracranial hypotension ($\chi^2 = 6.97$, df = 1, $P = 0.01$).

Post Hoc Subgroup Analysis

None of the demographics or clinical characteristics predicted any outcome measures except for the reason of inclusion in the study, which was related to the preference of a particular IR (Figure 1).

Six out of eight patients, who entered the study because side effects prohibited dose escalation of ITB, reported preference for FIRD because dystonia and pain improved (median PPQ score 2.5 [IQR –1.4–3.8]). All six patients, who entered the study because they did not respond to a minimum daily dose of 600 μg ITB without baclofen-related side effects, preferred SIRD, except one patient who reported no preference for any of the IRs (median PPQ score 2.0 [IQR 0.8–3.5]). Mann–Whitney *U* test revealed a significant difference in patient's preference ($P = 0.03$) between groups, stratified according to "reason of participation." No significant difference was found for any of the other primary and secondary outcomes as well as the rate or severity of adverse events between both groups ($P > 0.05$). The clinical assessor's guess of which IR was administered was correct in 57%.

Table 4 Difference in change for primary and secondary outcome measures

Measure	FIRD, median (IQR)	SIRD, median (IQR)	Δ FIRD–SIRD, median (IQR)	*P* value
Primary outcome measures				
NRS for dystonia	–0.6 (–1.3–0.2)	0.0 (–1.3–0.8)	–0.3 (–1.1–0.5)	NS
NRS for pain	–0.4 (–0.8–0.4)	0.0 (–1.8–0.2)	0.1 (–0.8–1.3)	NS
Secondary outcome measure				
Burke–Fahn–Marsden scale	0 (0–7)	–2 (–6–0)	2 (–4–13)	NS

Negative values represent improvement in outcome measures. *P* values were derived from a Wilcoxon signed rank test.
NS = not significant; FIRD = faster infusion rate delivery; SIRD = slower infusion rate delivery; IQR = interquartile range; NRS = numeric rating scale.

Table 5 Adverse events reported after each infusion rate treatment

Adverse event	SIRD	FIRD
Headache	1 (7)	5 (36)
Chorea	0	1 (7)
Nausea	1 (7)	1 (7)
Hallucinations	0	1 (7)
Short-term amnesia	0	2 (14)
Light-headedness	0	1 (7)
Drowsiness	0	1 (7)

Numbers represent N (%).
SIRD = slower infusion rate delivery; FIRD = faster infusion rate delivery.

Discussion

Intrathecal drug delivery has opened new avenues for the administration of drugs like baclofen that have difficulty passing the blood–brain barrier. However, once the drug is in the intrathecal space, many aspects may influence its profile of efficacy and safety [21]. One of these aspects is the IR of a drug, which surprisingly has barely been explored [17,18]. In a recent study on long-term effects of ITB in CRPS-related dystonia, we noted that a substantial percentage of patients, who responded to ITB during a screening procedure using an external pump, subsequently failed to respond to continuous ITB with an implanted pump [16]. These poor responders included patients who failed to improve ≥25% in global dystonia severity in spite of repeated dose escalations (up to 600 μg/24 hours) and patients in whom dose escalation was limited because of the occurrence of side effects. Interestingly, the intrathecal IR applied during the screening period exceeded the IR of the postimplantation period as much as seven times because a lower concentration (0.5 mg/mL) was used. Additionally, the daily dose at the time patients qualified for the responder criterion of the screening procedure was lower in the majority of patients compared with the daily dose administered during the postimplantation period (Table 1). Triggered by these findings, we evaluated if different IRs at a fixed daily dose influence the efficacy and safety of ITB in patients with CRPS-related dystonia. In addition to dystonia, we evaluated the influence of ITB on pain because baclofen may exert an analgesic effect [22]. Prior to the start of this study none of the patients experienced a beneficial response in pain to ITB. Both for the total group as well as the subgroups defined by reason of inclusion, we found no differences between FIRD and SIRD on any of the primary outcome measures. Blinding was adequately maintained, as the sequence of IRs was correctly guessed in approximately half of the cases. Our findings may indicate that IR differences up to a factor four do not account for the lack of response to ITB in implanted patients. Although we cannot exclude that the difference between the two IRs was too small to detect a clinically relevant difference, the use of a four-times higher IR seemed appropriate. The use of a concentration below 0.75 mg/mL would have implied

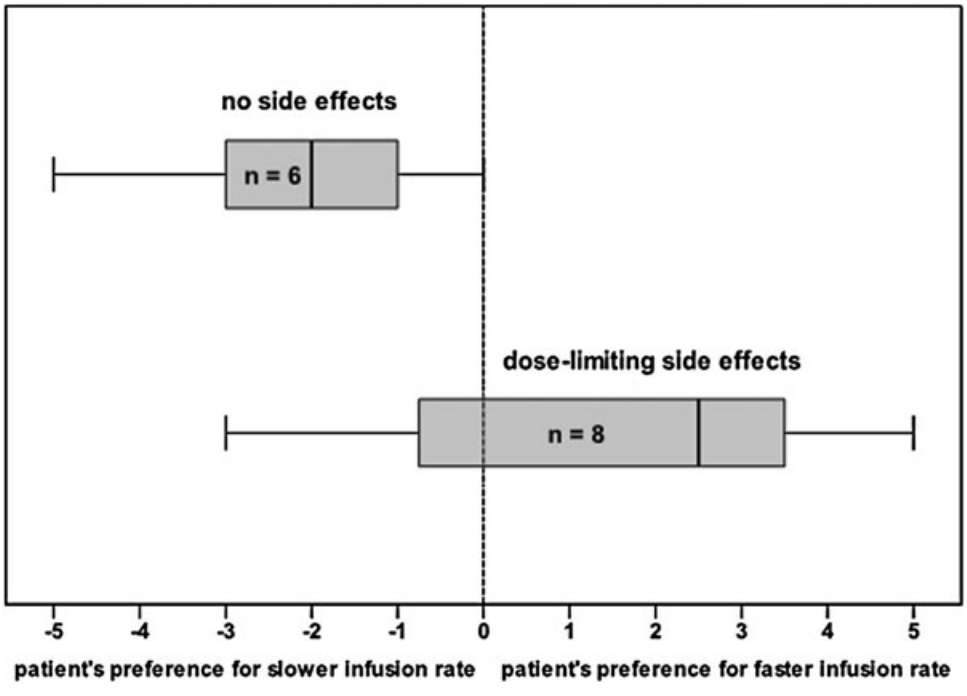

Figure 1 Box plot illustrating patient's preference for patients with a poor response with and without dose-limiting side effects.

an extra refilling of the pump during the FIRD period in some patients, which may have caused deblinding. The majority of patients displayed dystonia in all extremities reflecting the referral of more severely affected patients to our tertiary center. One could argue the severity of dystonia may account for the lack of response to ITB. However, only patients who had demonstrated responsiveness to ITB at an earlier stage were included in this study. Another limitation of this study could be the large variability in the daily administered dose of ITB across the patients, which reflects individual differences with respect to the dose of ITB at which patients perceived some albeit insufficient benefit (<25%) or the highest tolerated dose that did not cause unacceptable side effects. Consequently, it was not possible to equalize the daily administered dose of ITB. On the other hand, using a crossover design, patients served as their own controls with the daily dose fixed for each patient. Contrary to the primary outcomes, patient's preferences indicated significant differences with respect to the preferred IR. Except for one case, all patients who were included because they failed to respond to sequential dose escalations of ITB (without baclofen-related side effects) favored SIRD. Surprisingly, the majority of patients, who were included in the study because side effects restricted further dose escalation of ITB, reported a preference for FIRD. In a written statement delineating their preference, all but one patient in both subgroups revealed that their preference was based on the influence of the IR on dystonia and pain, which apparently outweighed the severity of adverse events.

Of note is that patients' preferences were paralleled neither by changes in primary and secondary outcome measures of dystonia nor by the clinical impression of change, which may question the responsiveness of the applied assessment scales to subtle changes. Possibly, increasing the IR under a fixed daily dose reduces the severity of side effects as compared with increasing the IR by raising the daily dose. In 11 patients, a screening procedure was performed prior to pump implantation. Interestingly, patients who participated in the study because ITB-related side effects limited dose escalation had a significantly larger difference between the IRs of the screening and postimplantation, compared with patients with a poor response without side effects (Table 6). All patients of the first category favored FIRD, except for one patient, who suffered from severe intracranial hypotension headache during FIRD and consequently preferred SIRD. However, it deserves emphasis that the aforementioned findings are the result of post hoc subgroup analyses and hence warrant further investigation in future studies. During the FIRD, patients reported significantly more adverse events of a supraspinal origin. As the daily dose of ITB was fixed for both IRs, this finding likely suggests a more extended intrathecal distribution of baclofen with higher IRs.

Conclusions

In conclusion under a fixed daily dose, a four-times higher IR enhances the intrathecal distribution of baclofen as evident from the significantly higher number of adverse events. However, in CRPS a fourfold higher IR is not associated with clinically overt improvement of dystonia or pain. Patients in whom side effects restricted further dose escalations of ITB favored FIRD because of subjective improvement of dystonia and pain. In these patients, FIRD did not cause more side effects than in patients who failed to respond to ITB after subsequent dose escalations but who had not experienced side effects. Consequently, in the subgroup of patients in whom side effects prevent ITB dose escalation, the effect of increasing the IR of ITB at a fixed daily dose should be further investigated.

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Conflicts of Interest

All authors report no financial interest on the subject matter or any competing materials. Sam Eldabe currently receives research funding from Medtronic and has also received honoraria for lectures given on Medtronic's behalf in the last year. Eric Buchser's employer, EHC Hospital of Morges, has received research and educational grants from Medtronic sàrl, Tolochenaz Switzerland. Jacobus Johannes van Hilten has been a consultant for Medtronic and has received an unconditional research grant from Medtronic.

Table 6 Ratios of drug delivery characteristics for screening vs postimplantation period

	Poor response with no side effects	Poor response with dose-limiting side effects	*z* Value	*P* value
Median (IQR) daily dose ratio	0.4 (0.3–0.6)	1.0 (0.6–1.2)	–2.19	0.03
Median (IQR) infusion rate ratio	2.6 (2.0–3.4)	5.6 (3.6–7.0)	–2.19	0.03

The screening to postimplantation period ratio for infusion rate and daily dose for patients with a poor response with and without side effects to intrathecal baclofen [16].
P values were derived from a Mann–Whitney *U* test.
IQR = interquartile range.

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