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Original Research Article

Randomized two dimensional between patient response surface pathway design with two interventional and one response variable in estimating minimum efficacy dose

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ABSTRACT

Background: The aim of this paper is to introduce and evaluate the RSP design with two interventional and one response variable exemplified by estimating minimum efficacy dose (MED) of osteopathic manual therapy (OMT) in treatment of gastroesophageal reflux disease (GERD).
Methods: 15 GERD patients, divided in three design-level with three, five and seven patients. The study was performed as a randomized two-dimensional, between-patient RSP designed multicenter study with two interventional– and one response variable. The interventional variables "Number of OMT's" and "Treatment Interval" with common response variable, formed two independent one-dimensional randomized between-patient RSP studies. The response variable was percent reduction in sum of the five GERD score from baseline. Three GERD patients were allocated on the first design level and given six OMT with five days' interval. Based on results obtained in the first and second design level, five patients were included to the second design level and seven to the third.
Results: The two-dimensional randomized between-patient RSP-design with the combined outcome procedure worked as expected. The percent reduction in GERD score increased with increasing number of OMT's and time intervals. This increase leveled out after three to five OMT's and three to four days between treatments. A clinical interaction between the two interventional variables was obtained. The estimated MED of OMT in treatment of GERD was three treatments with two days between treatments.
Conclusions: The suggested two-dimensional, randomized between-patient RSP-design worked as expected and estimated MED of OMT in GERD patient sufficiently.

Keywords: Two-dimensional randomized response surface pathway design, RSP, Osteopathic manual therapy, OMT in treatment of GERD, Dose-response

INTRODUCTION

For many years, antacids have been the treatment of choice related to gastroesophageal reflux disease (GERD) and peptic ulcers. The first breakthrough for pharmacological treatment came with the introduction of histamine-2 receptor (H2) antagonists in the 1970s, followed up with proton pump inhibitors (PPI) twenty

years later.[1] PPIs are now the gold standard in the treatment of GERD. The aim of medical therapy is to increase pH of the gastric juice and thus cure the esophagitis. However, GERD itself will not be cured, and most patients need continuous treatment to obtain adequate relief of symptoms.[2] Anti-reflux surgery, fundoplication, is an effective and curative approach, which has been performed laparoscopically with acceptable merits for the last decades.[3] Several minimally invasive operative methods, performed laparoscopically for the last decades have acceptable merits. However, the disadvantages of surgery include the risk of severe side effects, and irreversible procedural complications.

One possible reason accounting for the development of GERD might be failure of the lower esophageal sphincter (LES).[2] The role of osteopathy in understanding and treating the musculoskeletal system has been known for over a hundred years.[4] However, the effect of Osteopathic treatment on LES has previously been described.[5] This study demonstrated a positive increment of diaphragm stretching using breading techniques in the LES region. Osteopathic Manual Therapy (OMT) includes several techniques that might influence LES and enhancing its effect. OMT performed on uncomplicated GERD patients has earlier been described, demonstrating a promising effect in treatment of the disease.[6] A randomized double-blinded multicenter study has recently verified these results.[7] However, the dose OMT constitutes number- and time interval between each treatment and both variables have varied in earlier studies.[6,7] A dose-responds study aimed at estimating Minimum Efficacy Dose (MED) OMT in treatment of GERD is needed.

The choice of study design for interventional uncontrolled-, controlled- or randomized clinical trials (RCT) constitutes a challenge for researchers worldwide.[8,9] Ethical and scientific conduct, coupled with scarce resources, requires choice of a study design that combines a minimum of included patients whilst producing as strong statistical evidence as possible. These opposing goals makes the choice of an efficient study design capable of handling different combinations of interventions and measureable clinical outcomes in a challenging landscape critical.

"Response surface pathway" (RSP) design was introduced and developed in laboratory animal studies, and later for dose-response studies in animal and human cancer patients.[10-13] Both within- and between-patients RSP design has been introduced, but the procedure for allocating patients from one design level to the next was not optimal.[14] Further development of the RSP methodology was aiming to reduce the number of patient and simultaneously increasing statistical power behind the achieved study outcomes. The earlier RSP design version has focused on documentation in clinical trials without inclusion of randomization procedures, odd number of outcomes and combinations with other classical study designs. The rationale for increasing the number of subjects from one level to the next has been shown to optimize study design goals in LD50 studies in a laboratory setting. Such increase in number of patients from one design level to the next was solved by inclusion of randomization.[11,15]

Development of the RSP-method by combining it with other study designs has also been performed to increase the strength, versatility and practical usability of the study design methodology.[15] Combining the RSP design with other traditional study designs, made RSP applicable in both controlled- and randomized controlled clinical trials.

The optimization of the RSP design has mainly been performed with one interventional- and one response variable. By combining within- and between patients RSP the two-dimensional model with two interventional and one response variable has been developed.[16] The two-dimensional between-patient RSP-method with two interventional and one response variable as well as with one interventional and two response variables has so far never been developed and applied in clinical or laboratory animal trial.

The dose of OMT consists of number of treatments and time interval between treatments. The aim of this paper is to present the randomized, two dimensional between-patient RSP design with two interventional- and one response variable, demonstrated by estimating MED of OMT in treatment of GERD.

METHODS

This study was performed at five Norwegian Osteopathic clinics from September 2016 to April 2017 with one year follow-up. The patients were recruited from and treated at five Norwegian osteopathic clinics with Halden in south, Bergen in west, Hønefoss in east, Trondheim in the mid and Alta in north. The regional committee for medical and health research ethics (REC South East Norway) approved the study. The patients gave informed consent to participate.

The study was performed as a multicenter dose-response study of OMT in GERD patients by using a two-dimensional RSP design with one year follow-up.[15,16]

The study population consists of GERD patients of both genders, passed the age of 18 years with known effect of anti-reflux medication were included.[17,18] Patients with hiatus hernia ≥5 cm and patients suffering from gastric ulcer, cancer and uncontrolled bacterial, viral, fungal or parasite infection were excluded. The patients were recruited from and treated at five geographically widely spread Norwegian osteopathic clinics.

The study sample consisted of five male and 10 female GERD patients, all gastroscopically examined to exclude other diagnoses and patients with large hiatus hernia. The

material was divided in three design-levels with three, five and seven patients, respectively. The three groups of patients were found comparative regarding age, body weight and body-mass index (Table 1). Disease duration in the study sample was long, but substantially longer among patients in the first design level.

Table 1: Material description within each design levels; the results expressed by mean values, standard deviation in brackets and total range.

Factors	Design level 1 (n=3)	Design level 2 (n=5)	Design level 3 (n=7)
Age (years)	52.8 (11.2) 44.8–65.6	49.6 (20.1) 25.7–71.5	49.6 (17.3) 27.2–75.7
Body weight (kg)	74.2 (13.2) 63.6–89.0	68.8 (13.5) 52.0–85.0	69.0 (18.3) 47.0–105.0
Body mass index (kg/m^2)	24.6 (3.2) 19.8–28.7	23.2 (2.5) 17.6–27.4	24.8 (2.1) 18.4–37.7
Disease duration (Years)	26.5 (14.0) 10.4–36.3	3.2 (4.0) 0.2–10.0	9.7 (3.3) 0.4–26.2

Study performance

The study was conducted as a two-dimensional, randomized between-patient three-level RSP designed multicenter study with two interventional– and one response variable. Each of the interventional variables together with common response variables formed two independent one-dimensional randomized between-patient RSP studies [15]. The two interventional variable were "Number of OMT's" ranging from one to 12 and "Interval in days between each treatment" ranging from one to 10 days. One-day treatment interval equals 24 hours. The mid-value strategy with six OMT's (M=6) and five days' intervals (L=5) were used at the first design level.

The five GERD variables recorded at baseline and one week after the last treatment were degrees of "Heartburn", "Chest pain", "Acid in mouth", "Epigastric pain" and "Thoracic pain", each recorded on a 10 cm visual analogue scale (VAS). The response variables in both the two RSP designed studies were percent reduction in sum of the five GERD variables from baseline. This response variable was in the study design categorized as 1) <25% reduction, 2) [25–50% >reduction, 3) [50–75% >reduction and 4) [75–100%] reduction. MED of OMT was defined to give minimum 50% reduction in the sum of GERD score.

Each of the two one- dimensional RSP designs consisted of three dose levels. Three GERD patients allocated to the first design level received six OMT with five days' interval. Based on the results obtained from the first design level, five patients were subsequently included to the second design level. The number of OMT's (Table 2) and interval between each treatment (Table 3) was separately determined. Seven patients were included to the third design level and given the number of OMT's and interval between treatments calculated based on results obtained from the second design level.

Table 2: Changes in number of osteopathic manuel treatments (OMT) from one design level to the next within a window from 1 to 12 OMT based on the obtained reduction in sum of gastro esophageal reflux disease (GERD) score measured on 10 cm visual analogue scale (VAS).

Number of treatments design level 1 M_1=m	Outcome variable design level 1 Sum VAS % reduction	Number of treatments design level 2 M_2	Outcome variable design level 2 Sum VAS % reduction	Number of treatments design level 3, M_3
m (6 treatments)	< 25	m+m/k (10 treatments)	<25	m+m/k+m/k^2 (12 treatments)
			[25–50]	m+m/k+m/k^3 (11 treatments)
			[50–75]	m+m/k–m/k^3 (8 treatments)
			[75–100]	m+m/k–m/k^2 (7 treatments)
	[25–50]	m+m/k^2 (8 treatments)	<25	m+m/k^2+m/k^3 (10 treatments)
			[25–50]	m+m/k^2+m/k^4 (9 treatments)
			[50–75]	m+m/k^2–m/k^4 (7 treatments)
			[75–100]	m+m/k^2–m/k^3 (6 treatments)
	[50–75]	m-m/k^2 (4 treatments)	<25	m–m/k^2+m/k^3 (6 treatments)
			[25–50]	m–m/k^2+m/k^4 (5 treatments)
			[50–75]	m–m/k^2–m/k^4 (3 treatments)
			[75–100]	m–m/k^2–m/k^3 (2 treatments)
	[75–100]	m-m/k (2 treatments)	<25	m–m/k+m/k^2 (5 treatments)
			[25–50]	m–m/k+m/k^3 (4 treatments)
			[50–75]	m–m/k–m/k^3 (2 treatments)
			[75–100]	m–m/k–m/k^2 (1 treatment)

Table 3: Changes in duration between treatments from one design level to the next within a window from 1 to 10 days based on the obtained reduction in sum of gastro esophageal reflux disease (GERD) score measured on 10 cm visual analogue scale (VAS).

Duration between treatments design level 1 L_1=l	Outcome variable design level 1 Sum VAS % reduction	Duration between treatments design level 2 L_2	Outcome variable design level 2 Sum VAS % reduction	Duration between treatments design level 3 L_3
l (5 days)	<25	l+l/k (8 days)	<25 %	l+l/k+l/k^2 (10 days)
			[25–50]	l+l/k+l/k^3 (9 days)
			[50–75]	l+l/k–l/k^3 (7 days)
			[75–100]	l+l/k–l/k^2 (6 days)
	[25–50]	l+l/k^2 (7 days)	<25	l+l/k^2+l/k^3 (9 days
			[25–50]	l+l/k^2+l/k^4 (8 days)
			[50–75]	l+l/k^2–l/k^4 (6 days)
			[75–100]	l+l/k^2–l/k^3 (5 days)
	[50–75]	l–l/k^2 (3 days)	<25	l–l/k^2+l/k^3 (5 days)
			[25–50]	l–l/k^2+l/k^4 (4 days)
			[50–75]	l–l/k^2–l/k^4 (2 days)
			[75–100]	l–l/k^2–l/k^3 (1 day)
	[75–100]	l–l/k (2 days)	<25	l–l/k+l/k^2 (4 days)
			[25–50]	l–l/k+l/k^3 (3 days)
			[50–75]	l–l/k–l/k^3 (1 day)
			[75–100]	l–l/k–l/k^2 (1 Day)

Response surface pathway (RSP) design

This is an adaptive design and the methodology has previously been presented within- and between-patients with one interventional- and one response variable.[14] Development of the methodology in laboratory animals and simulations demonstrated that allocation of equal number of subjects to each level is not an optimal solution.[11] By starting with a low number of patients at first design level and increase this number with increased level, the sample size reduces without reduction in accuracy.[15]

Dose adjustments procedures in RSP design

Let M=m denote the starting dose, m_i the dose at design level i, and k the dose adjustment factor. The dose at design level i given by equation (1). Let D_u denote the upper limit of the interventional variable and n the number of design levels, then D_u given as the sum of a geometric series in equation (2).[19]

$$(1) \qquad m_i = m_{i-1} \pm \frac{m}{k^{i-1}} : \ i = 1, 2 \ldots . n$$

$$(2) \qquad D_U = \frac{m\left(k^n - 1\right)}{\left(k^n - k^{n-1}\right)}$$

With known upper limit of the interventional variable, the starting value m and design level n, the k-adjustment factor calculates from equation (2).

Escalation and de-escalation procedure

Both the response variables in the present model are multinomial with equal number of categories denoted as 2c. Of these possible 2c response values, c gives escalation and the remaining c de-escalation of the interventional variable for the patients in the next design level. The predefined window of the interventional variable is denoted as D_U=the upper and D_L=the lower limit. It may be convenient to use the mid value of the predefined dose window as the starting value. To ensure coverage of the dose window the mid value strategy is chosen and a dose adjustment procedure established. Assume the response variable have a sample space {1,2…2c}. Let *i* represent the new design level, *j* the outcome from the previous dose level *i-1* and *h* the outcome resulted in dose level *i-1*. For calculation of the second dose level $h \equiv 1$ per definition, then for design level $i \geq 2$ the interventional value is given as:

$$(3)\ m_i = m_{i-1} + m_1/k^{i+j+h-2c+1} \ ; \ j \leq c \ \& \ h \leq c$$
$$m_i = m_{i-1} - m_1/k^{i-j+h+2c-2} \ ; \ j > c \ \& \ h \leq c$$
$$m_i = m_{i-1} + m_1/k^{i+j+h-2c} \ ; \ j \leq c \ \& \ h > c$$
$$m_i = m_{i-1} - m_1/k^{i-j+h+2c-3} \ ; \ j > c \ \& \ h > c$$

Combination of randomization based on the outcome results

Let M_1, M_2 and M_3 denote the RSP-calculated "Number of OMT" used at the second design level (Table 2) and L_1, L_2 and L_3 denote the similar for "interval between treatments" (Table 3). For second design level, the

number of combinations to randomize for the five patients will then be 3^2=9. From the obtained combinations, the OMT given the five patients on second design level were randomly allocated with replacement. The similar procedure performs for the third design level.

Let M_1, to M_5 denote the RSP-calculated "Number of OMT" obtained from design level 2 (Table 2) and L_1 to L_5 the similar for "Interval between treatments" (Table 3). The number of combinations randomized for the seven patients on third design level will then be 5^2=25.

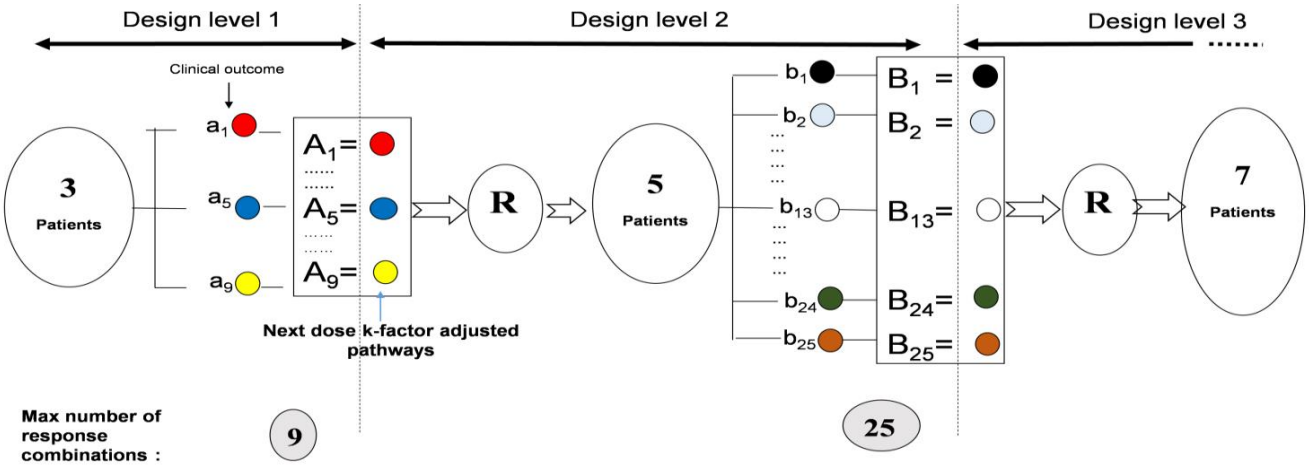

Figure 1: Randomization procedure.

Notes: Small letters a_1–a_9 and b_1–b_{25} indicate the numbers within each response category. A_1–A_9 and B_1–B_{25} represent dose to be used in next design level. The nine possible clinical responses from the patients in the first design level point to the next k-factor adjusted dose recommendation for second design level. Similarly from second to third design level. "R" represents randomization from one design level to the next.

Randomized between-patient RSP design

To optimize the RSP model, the number of included patients are reduced to a minimum ≥2 at the first design level and increasing with design level. A previously recommend procedure is to include three subjects at the first level and increase to 5, 7, 9 etc. at the second level and upwards.[14,15] The three patients allocated to the first design level received six OMT's with five days' interval between treatments. Assuming a_1 represents number of patients at first design level pointing out the A_1 combination of numbers of OMT's and intervals between treatments for the second design level, a_2 pointing out the combination A_2, a_3 the combination A_3, and upward to a_9 pointing out the combination A_9 (Figure 1). In general, a weighted randomization in ratio (a_1:a_2:a_3….:a_9). If five of the nine possible combinations in number of OMT's and intervals between treatments are equal (A_1=A_2=A_3=A_4=A_5) and the other are different, the patients on second level will be weighted randomized (5:1:1:1:1) with replacement.

Based on the percent reduction in sum of the five GERD score obtained in the five patients on the second design level, 25 new combinations of numbers of OMT's and intervals between treatment (B_1;B_2;….B_{25}) constitutes the possible treatment regime for the seven patients in third design level (Figure 1). Assuming b_1 patients at the second design level calculated by the RSP procedure to receive the combination B_1, b_2 to receive the combination B_2, and upwards to b_{25} to receive the combination B_{25}.

The combination of number of OMT's and intervals between treatment to be used at third design level for the seven new patients will be allocated by weighted complete randomization (b_1:b_2:b_3:...b_{25}) with replacement following the same procedure as described for the second design level above.

Statistical analysis

Sample space for number of OMT's may be expressed as Ω_{omt} = {D_{Lomt}≤….≤D_{Uomt}} and for intervals between treatments as Ω_{int} = {D_{Lint} ≤….≤D_{Uint}}. MED of OMT is defined to give minimum 50% reduction in the sum of GERD score. Let μ represents MED for GERD patients and assume μ covers by [Ω_{omt} U Ω_{int}]. The percent reduction in sum of GERD score are ordinal in both the two interventional variables and the probability assumes monotonically increase over the interventional levels. Isotonic regression was used for estimation of MED.[20-22] Continuously distributed variables are expressed by mean values, Standard deviation (SD) in brackets and 95% confidence interval.[23]

RESULTS

Three patients received six OMTs with five days' interval between each treatment (6×5) and obtained a reduction in the sum of GERD symptoms above 50% (Figure 2 and 3). The results from two patients recommend (4×3) OMT's and (2×2) from one patient. Number of possible combinations for randomization at the second design

level was 3^2=9. Based on these results, the background for randomization consisted of (4×3) four times, (4×2) two times, (2×3) two times and (2×2) once. The randomization with replacement resulted in two patients receiving (4×3), two patients (4×2) and one (2×3). At the second design level, two patients obtained a reduction in GERD score between 50 and 75% and three patients a reduction above 75% (Figure 2 and 3).

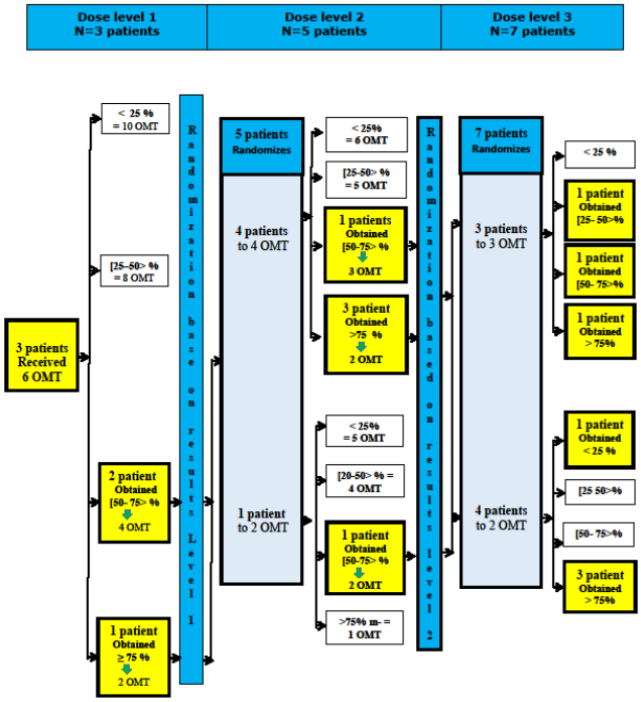

Figure 2: Allocation of patients to receiving number of OMT's in the three design levels. Yellow boxes give number of patients with obtained results and recommended number of OMT's for the next design level. Grey boxes give results of randomization based on results from previous design level.

The results obtained from two patients recommend (2×1); from one patient (2×2) and from two patients (3×1). Based on these results the combinations for randomization at the third design level was 5^2=25 possibilities; nine times (2×1), six times (2×2), six times (3×1) and four times (3×2). The randomization with replacement resulted in two patients receiving (2×1), two receiving (2×2), two receiving (3×1) and one (3×2). One patient at the third design level receiving three OMTs and one receiving two OMTs obtained a reduction in GERD score below 50% and classified as non-responder in accordance with the definition (Figure 2). The estimated number of OMTs for obtaining responder to the GERD treatment was two OMTs with a 95% confidence interval from 1.44 to 2.41 which gives [1-3] (Figure 2).

The three patients receiving OMTs with an interval of two days all obtained a GERD reduction above 50%, but two of the four patients with an interval of 1 day was classified as non-responders (Figure 3). The estimated duration between the OMT's for obtaining responder was one day with 95% confidence interval from 0.61 to 1.18 which gives [1-2]. The MED of OMT in treatment of GERD consists of both the number and the interval duration. The combination closest with probability above 50% was (3×2). Consequently, MED of OMT in treatment of GERD was three OMT's with two days' interval between treatments. This resulted in a sum GERD score reduction of 62.2% with a 95% confidence interval from 50.3 to 80.1%.

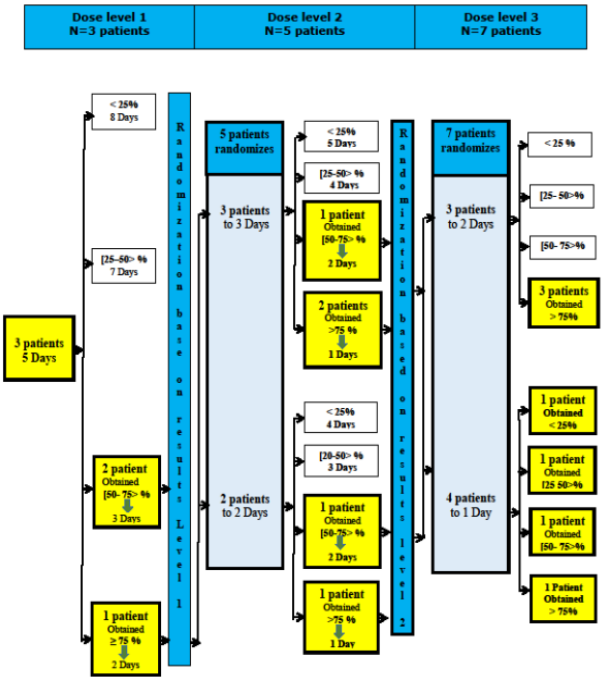

Figure 3: Allocation of patients receiving OMT related to treatment intervals in the three design levels. Yellow boxes give number of patients with obtained results and recommended treatment interval for the next design level. Grey boxes gives results of randomization based on results from previous design level.

The percent reduction in sum GERD score increases both with increasing number of OMT and treatment interval. However, this increase seems to level out after three to five OMTs and two to four days´ treatment intervals. The interaction between number of OMT and treatment intervals is clear (p=0.09). Treatment intervals and number of OMT's explained 32.5% and 13.9% of the variation in reduced sum GERD symptoms, respectively. The two variables with interaction explained 42.8% of the variation.

DISCUSSION

Dose-response studies are mainly performed for new pharmaceuticals, but recently also introduced in manual therapy.[24,25] The number of treatments and the interval between treatments usually specifies the dose in the field of interventional medical treatment. The doses used in

manual therapy are predominantly not based on results obtained from controlled clinical trials, but on practical experience. Clinical experience is very important, but to ensure optimal treatment effects, dose-response and RCTs are needed. Usually in dose-response studies, it is common to use one interventional- and one response- or outcome variable. With equal number of patients at each design level, between-patient RSP design can easily, but not optimally be performed.[12,14] To optimize the between-patient RSP design, a procedure for increasing the number of patients with increasing design level is needed.[11] Inclusion of randomization between design levels was recently introduced in a one-dimensional between-patient RSP.[15] This study additionally introduced odd number of outcomes and demonstrated flexibility in the RSP model and related randomization procedure. The same randomization procedure was also used in a two-dimensional RSP designed RCT combining within- and between-patient strategies.[16] Despite challenging clinical conditions, this study demonstrated valuable estimations indicating robustness of the RSP design. However, the combination of within- and between-patient requested use of randomization procedure only in one dimension.

The present paper introduces a two-dimensional between-patients RSP design with two interventional- and one response variable and increasing sample size with increase in design level. This requests randomization based on the same response variable in both dimensions. This was solved by RSP-calculating the recommended number of OMT's and duration of the treatment intervals for the next design level separately for each patient. The 3^2=9 and the 5^2=25 combinations from the first and the second design levels were used as the basis for randomization in the second and third design levels, respectively. In this way, all possible combinations based on obtained results from previous design levels were included. The randomization worked in accordance with intention and resulted in estimation of both the interventional parameters with sufficient accuracy. However, the 95% confidence interval of the estimated MED was a bit too large. The number of patients and the increasing procedure was based on simulations, but only in the one-dimensional situation [11]. In the two-dimensional situation with dependent interventional variables and the suggested randomization background, a sample size of 15 patients is too low. By using five patients at the first design level and increasing to seven and nine at the next two levels might have given sufficient accuracy in the estimation of MED.

The combination procedure used in this study covers the entire possible outcome-window based on previous design levels and always gives 9 and 25 possibilities for second and third design level. Another possible procedure is only to use the recommended combinations from the previous design level. The basis for randomization will then be reduced to three and five for the second and third level, respectively. Such a procedure optimizes the dependency between recommended number of OMT's and interval duration from each previous patient and obtains a sample size situation equal to the one-dimensional situation.[11] However, several important combinations of the two-interventional variable approach may disappear. In the present study, the combination (3×2) will not be included at the third design level and was the combination found to be MED of OMT in treatment of GERD. The combination procedure introduced in the present study seems to be a better choice, but requires an increase in sample size. A new simulation of the power equal to the one performed in the one-dimensional situation [11] is recommended for two interventional- and one response variable studies.

The aim of this study was to estimate MED of OMT in treatment of GERD. This aim was successfully addressed and the study unlocked understanding important for further development of the methodology. Reduction in the sum of GERD score increases when the number of OMTs increased from two to five, but then seem to flatten out. This may indicate that the treatment has taken out all the positive clinical effects up to five OMTs. The effect increased with increasing number of OMTs, but the obtained increase was not convincing only based on the dose-response results. Inclusion of the observation performed after each OMT gave a better picture. The dominant of the two interventional variables seem to be duration interval between OMTs. The OMT effect increased significantly with increasing duration, but obtained a maximum between three and four days. The mechanism of action for OMT in treatment of GERD may explain this development. Most of the included patients have suffered from GERD many years and it might be that the closing mechanism between esophagus and stomach in a way has been "frozen". OMT in this study is directly related to this closing mechanism. It is possible that the sphincter starts working again only after a few OMTs if the interval between each treatment is reasonably short. The present study estimated MED and OMT in treatment of GERD, but studies documenting optimal efficacy dose (OED) is needed. By using the obtained results from this study, a new dose-response study aiming at estimation of OED can be performed using a two-dimensional within- and between-patients RSP design.[16] The obvious choice would be to use the interval between OMTs as the interventional variable in the randomized between-patient part and number of OMTs in the within-patient dimension. The obtained results from the present study may also indicate a dose window for the OMT intervals in an OED-study either to be from two to four days or from one to five days. The mid-value strategy for the first design level would then give three day in both situations. However, the present results indicate a starting value of two days between treatments based on estimated MED. Such a choice would give a skewed starting point with regard to dose window. To ensure coverage of this window, a new procedure to the RSP-design must be developed.

CONCLUSION

The suggested randomized two-dimensional between-patient RSP-design with the combination procedures for the outcomes worked as expected and estimated MED of OMT in GERD patient sufficiently. The accuracy of the estimates will improve by increasing the sample size, which seem underestimated in this study.

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