Comparison of Hemorrhoidal Treatment Modalities

A Meta-Analysis

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PURPOSE: The purpose of this study was to assess whether any method of hemorrhoid therapy has been shown to be superior in randomized, controlled trials. METHOD: A meta-analysis was performed of all randomized, controlled trials assessing two or more treatment modalities for symptomatic hemorrhoids. Outcome variables included response to therapy, need for further therapy, complications, and pain. RESULTS: A total of 18 trials were available for analysis. Hemorrhoidectomy was found to be significantly more effective than manual dilation of the anus ($P = 0.0017$), with less need for further therapy ($P = 0.034$), no significant difference in complications ($P = 0.60$), but significantly more pain ($P < 0.0001$). Patients undergoing hemorrhoidectomy had a better response to treatment than did patients treated with rubber band ligation ($P = 0.001$), although complications were greater ($P = 0.02$) as was pain ($P < 0.0001$). Rubber band ligation was better than sclerotherapy in response to treatment for all hemorrhoids ($P = 0.005$) as well as for hemorrhoids stratified by grade (Grades 1 to 2; $P = 0.007$; Grade 3 hemorrhoids, $P = 0.042$), with no difference in the complication rate ($P = 0.35$). Patients treated with sclerotherapy ($P = 0.031$) or infrared coagulation ($P = 0.0014$) were more likely to require further therapy than those treated with rubber band ligation, although pain was greater after rubber band ligation ($P = 0.03$ for sclerotherapy; $P < 0.0001$ for infrared coagulation). CONCLUSION: Rubber band ligation is recommended as the initial mode of therapy for Grades 1 to 3 hemorrhoids. Although hemorrhoidectomy showed better response rates, it is associated with more complications and pain than rubber band ligation, thus should be reserved for patients who fail to respond to rubber band ligation. [Key words: Hemorrhoids; Meta-analysis; Hemorrhoidectomy; Rubber band ligation; Injection sclerotherapy; Infrared coagulation]

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Many modes of therapy have been advocated for the treatment of symptomatic hemorrhoids unresponsive to diet or application of local preparations. These include injection sclerotherapy (IS), cryotherapy, rubber band ligation (RBL), infrared photocoagulation (IRC), diathermy, internal sphincterotomy, manual dilation of the anus (MDA), and surgical hemorrhoidectomy (SH). Although each type of therapy has its proponents, no single therapy has been proven to be superior. The explanation for this finding is either that there is actually no difference between the various treatments or that the published, randomized trials do not have sufficient power to show a statistically significant difference between the treatments compared when one does exist (Type II error).[1] Meta-analysis is a tool available to help circumvent these problems. "Meta analysis is a quantitative, systematic summary of a collection of separate studies for the purpose of obtaining information that cannot be derived from any of the studies alone."[2] Meta-analysis allows one to combine data from several studies to increase the statistical power of the analysis and compare various modalities. A meta-analysis of all published, randomized trials comparing two or more treatment methodologies for symptomatic hemorrhoids was undertaken to assess effectiveness of the various modes of therapy available.

METHODS

Criteria for inclusion in this meta-analysis were published trials in which patients were randomly allocated to two or more treatment methods for hemorrhoidal disease other than diet or topical preparations, with documentation of clinically relevant outcome measures. A minimum period of six months of follow-up was required. A computerized search (MEDLINE) from 1966 through February 1994 was undertaken using the Medical Subject Heading, hemorrhoids. The set was limited to clinical trials, multicenter studies, or randomized, controlled trials. A text word search using the term "random:" was also performed and combined with the Medical Subject Heading, "hemorrhoids," to increase sensitivity. Articles were then retrieved, and reference lists in the articles

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were reviewed to search for studies not retrieved by the MEDLINE search. Finally, the reference list of the "Hemorrhoid" chapter in two colon and rectal surgery texts[3, 4] was perused for any further articles, as was the index of this journal, *Diseases of the Colon and Rectum*, from 1966 to present. Treatment methods included injection sclerotherapy, rubber band ligation, infrared coagulation, cryotherapy, diathermy, ultroid, anal dilation, internal sphincterotomy, and operative hemorrhoidectomy. Two reviewers examined the Methods section of each of the articles, without examining the Results. Inclusion and exclusion from the review was established by consensus.

Trials were appraised using a 5-point score, modified from a scoring system reported by Solomon and McLeod.[5] Points were assigned if patients were randomized, exclusions were specified and appropriate, outcomes were measured objectively, raw data were accessible, and follow-up was complete. Items that did not affect entry of data into the meta-analysis, such as the statistical analysis used or whether a power analysis was done were removed from the rating scale. This was then followed by an overall judgment of the quality of the paper from one to five. All studies were reviewed by one reviewer (HMM). Interobserver reliability was assessed in a sample of the studies by a second reviewer (RSM).

Data were extracted by one reviewer (HMM), with interobserver agreement on the data extracted again being assessed in a sample of the studies. Results at 12 months were used for trials with greater than one-year follow-up. The methodology of each trial was documented as were data on patients enrolled. Outcome variables that were analyzed included the response to treatment (overall and by grade of hemorrhoid, when possible), the need for further treatment, complications of therapy, and pain.

Statistical analysis was done using a Mantel-Haenszel approach, with a series of 2 × 2 tables for each comparison.[6] Direct comparison of patients between trials was avoided because pooling of raw data may be misleading.[6, 7] The summary statistic used was the odds ratio. The odds ratio represents the odds of an adverse event occurring in the treated group compared with the control group. Thus, an odds ratio of less than one favors the treatment group. This statistic was chosen because of its statistical properties and widespread use in meta-analyses.[6] A fixed effect model was used in the analysis; thus, inference is conditional on the studies that have been done.[6] For each comparison, the within trial odds ratios and confidence intervals were computed, followed by the Mantel-Haenszel chi-squared test of significance. Finally, the pooled odds ratio using the Mantel-Haenszel method, which takes effect size into account, was computed. z values were added (Stouffer's z test) to test the significance of pooled results.[6, 7] Homogeneity was assessed with the Breslow-Day method,[8] ensuring that clinical homogeneity of patient population, treatment, and endpoints was also present.

RESULTS

A total of 32 randomized trials comparing two or more modalities of hemorrhoid therapy were identified. Excluded trials[9–19] and reasons for exclusion are listed in Table 1. Of the remaining 21 trials, the same data set was used for two studies in three cases,[20–25] leaving 18 distinct studies for analysis. Modalities assessed in two or more trials included hemorrhoidec-

Table 1.
Excluded Trials

Study	Modes of Therapy	Reason for Exclusion
Hood and Alexander-Williams[9]	MDA *vs.* RBL	One-month follow-up
Varma *et al.*[10]	Ultroid *vs.* IS	6-week follow-up
Wright *et al.*[11]	Ultroid *vs.* sham	16-week follow-up
Andrews *et al.*[12]	Scissors *vs.* diathermy excision	4-week follow-up
Griffith *et al.*[13]	Diathermy *vs.* RBL	2–5-month follow-up
Senagore *et al.*[14]	Scalpel *vs.* Nd:YAG laser	6-week follow-up, efficacy not specified
Reid Neto *et al.*[15]	Open *vs.* semi-open SH	3-month follow-up, efficacy not specified
Roe *et al.*[16]	Submucosal *vs.* open SH	6-week follow-up, limited outcome measures
Hinton and Morris[17]	Ultroid *vs.* bipolar	Follow-up not specified, limited outcome measures
Smith *et al.*[18]	SH *vs.* cryodestruction	Hemorrhoids, not patients, randomized
Wang *et al.*[19]	Laser *vs.* conventional SH	Randomization inadequate

Table 2.
Trials Included in Meta-Analysis

Study	No. of Patients		Months of Follow-up	Mean Age	Males	Females	Hemorrhoid Grade		Treatment
	Enrolled	Completed					Grade 1–2	Grade 3	
Murie *et al.*[20]	100	88	12	52	57	33	32	56	RBL, SH
Walker *et al.*[22]	200	151	48	47			200		IRC *vs.* RBL/IS
Anscombe *et al.*[29]	100	94	6	46	71	29	36	64	SH, MDA
Chant *et al.*[30]	54	51	6.7	47	26	25		51	SH, MDA
Lewis *et al.*[31]	112	108	24	47	61	51	46	66	SH, MDA, RBL, cryotherapy
Cheng *et al.*[32]	120	120	12	44	64	56		120	SH, MDA, RBL, IS
Hiltunen and Matikainen[33]	63	63	12	44				63	SH, MDA, sphincterotomy
Hardy *et al.*[34]	20	20	12	56	20		12	8	SH, MDA
Ambrose *et al.*[35]	135	94	12	45	74	61	135		IS, IRC
Gartell *et al.*[36]	269	214	33	49	171	98	177	42	IS, RBL
Greca *et al.*[37]	82	61	12		50	32	7	75	IS, RBL
Sim *et al.*[24]	50	46	12	45	33	13	46		IS, RBL
Ambrose *et al.*[38]	268	169	12	46	159	119	268		RBL, IRC
Templeton *et al.*[39]	137	120	12	46	97	40	137		RBL, IRC
Keighley *et al.*[40]	142	127	12	44	107	35			RBL, MDA, cryosurgery, sphincterotomy
Arabi *et al.*[41]	100	91	6	46			91		RBL, sphincterotomy

Table 3.
MDA *vs.* Hemorrhoidectomy

Source	No. of SH	No Response to Therapy					Require Further Therapy				Complications				Pain			
		MDA	SH	MDA	OR*	*P*	SH	MDA	OR*	*P*	SH	MDA	OR*	*P*	SH	MDA	OR*	*P*
Anscombe *et al.*[29]	47	46	1	6	0.14	0.04	3	0	0.14	0.13	4	13	0.36	0.06	7	1	7.7	0.03
Chant *et al.*[30]	24	27	2	11	0.13	0.009	0	4	0.12	0.11								
Lewis *et al.*[31]	26	29	0	4	0.12	0.10	5	7	0.75	0.66	6	3	2.6	0.21	26	3	454	<0.001
Cheng *et al.*[32]	30	30	1	3	0.31	0.30					6	0	15	0.02	22	1	80	<0.001
Hiltunen and Matikainen[33]	21	21	2	6	0.25	0.1	1	2	0.20	0.13								
Hardy *et al.*[34]	10	10	0	2	0.20	0.30	0	2	0.20	0.30	2	0	5	0.30	10	0	400	<0.001
Overall	159	163			0.18	0.002			0.16	0.03			0.98	0.60			50.7	<0.001

* Odds ratio (OR) <1 favors hemorrhoidectomy.

Table 4.
Rubber Band Ligation *vs.* Hemorrhoidectomy

Source	No.		All Grades No Response to Therapy				Grade 3 Hemorrhoids No Response to Therapy				Complications				Pain			
	SH	RBL	SH	RBL	OR*	*P*	SH	RBL	OR*	*P*	SH	RBL	OR*	*P*	SH	RBL	OR*	*P*
Murie *et al.*[20]	45	44	3	6	0.54	0.42	0	2	0.17	0.21	6	4	1.5	0.55	35	0	303	<0.001
Lewis *et al.*[31]	26	28	0	16	0.01	<0.001	Cannot separate by grade				6	2	3.9	0.10	26	8	130	<0.001
Cheng *et al.*[32]	30	30	1	1	1.0	1.0	1	1	1.0	1.0	6	0	16.2	<0.001	22	2	38	<0.001
Overall	101	102			0.17	0.001			0.40	0.17			3.2	0.02			93	<0.001

* Odds ratio (OR) <1 favors hemorrhoidectomy.

Table 5.
Rubber Band Ligation *vs.* Sclerotherapy

Source	No.		All Grades No Response to Therapy				Grade 1–2 Hemorrhoids No Response to Therapy				Grade 3 Hemorrhoids No Response to Therapy				Require Further Therapy				Complications				Pain			
	IS	RBL	IS	RBL	OR*	*P*	IS	RBL	OR*	*P*	IS	RBL	OR*	*P*	IS	RBL	OR*	*P*	IS	RBL	OR*	*P*	IS	RBL	OR*	*P*
Gartell *et al.*[36]	109	105	35	11	0.25	0.001	31	7	0.20	0.0001	4	4	0.45	0.33	27	7	0.25	0.001	0	1	3.1	0.53	0	0	0.003	0.98
Cheng *et al.*[32]	30	30	6	2	0.11	0.09					6	2	0.11	0.02					2	0	0.20	0.26	0	2	5.4	0.24
Greca *et al.*[37]	33	28	10	10	1.3	0.20	Cannot separate results by grade								4	2	1.2	0.75	2	1	0.57	0.19	0	3	9.2	0.08
Sim *et al.*[24]	24	22	6	6	1.1	0.86	6	6	1.1	0.86					5	5	1.1	0.88	4	2	0.60	0.58	3	6	2.6	0.21
Overall	196	176			0.43	0.005			0.33	0.007			0.25	0.04			0.45	0.03			0.63	0.35			3.5	0.03

* Odds ratio (OR) <1 favors RBL.

Table 6.
Rubber Band Ligation *vs.* Photocoagulation

Source	No.		No Response to Therapy				Require Further Therapy				Complications				Pain			
	IRC	RBL	IRC	RBL	OR*	*P*	IRC	RBL	OR*	*P*	IRC	RBL	OR*	*P*	IRC	RBL	OR*	*P*
Ambrose *et al.*[38]	90	79	27	20	0.79	0.46	36	11	0.23	0.0001	2	5	3.0	0.18	0	6	14.5	0.02
Templeton *et al.*[39]	58	62	7	5	0.64	0.47					1	1	0.93	0.96	3	15	5.4	0.24
Walker *et al.*[22]	43	35	6	4	0.80	0.11	5	2	0.46	0.37	10	6	0.68	0.51	4	21	4.6	0.0001
Overall	191	176			0.76	0.29			0.26	0.0014			1.1	0.48			9.8	0.0001

* Odds ratio (OR) <1 favors RBL.

Table 7.
Sclerotherapy *vs.* Photocoagulation

Source	No.		No Response to Therapy				Require Further Therapy			
	IS	IRC	IS	IRC	OR*	*P*	IS	IRC	OR*	*P*
Ambrose *et al.*[35]	42	52	11	9	0.59	0.30	6	12	1.8	0.22
Walker *et al.*[22]	35	38	4	1	0.21	0.14	1	2	1.9	0.61
Overall	77	87			0.48	0.10		1.8	0.27	

* Odds ratio (OR) <1 favors photocoagulation.

tomy, manual dilation of the anus, internal sphincterotomy, photocoagulation, sclerotherapy, rubber band ligation, and cryotherapy. Bipolar diathermy,[26] scissors *vs.* diathermy excision,[27] and maximum anal dilation combined with hemorrhoidectomy[28] were assessed in only one study each, and, thus, meta-analysis could not be done. The 16 trials included, along with data on the patients enrolled, are listed in Table 2. The following comparisons were amenable to meta-analysis as patients were randomized to the treatment groups in a minimum of two trials: MDA *vs.* SH (six trials),[29–34] RBL *vs.* SH (three trials),[20, 31, 32] IS *vs.* IRC (two trials),[22, 35] IS *vs.* RBL (four trials),[24, 32, 36–37] and RBL *vs.* IRC (three trials).[22, 38, 39] RBL *vs.* cryotherapy,[31, 40] RBL *vs.* MDA,[32, 40] RBL *vs.* sphincterotomy,[40, 41] cryotherapy *vs.* MDA,[31, 40] and MDA *vs.* sphincterotomy[33, 40] were also amenable to comparison; however, these showed significant heterogeneity.

Mean global assessment of study quality was 2.5 ± 0.6, with an unweighted kappa for interreviewer assessment of overall study quality of 1.0. For the 5-point scale, the unweighted kappa for interrater agreement was 0.70.[42] Agreement on data extraction in a sample of studies was 87 percent.

Overall results of response to therapy, need for further therapy, complications, and pain were compared for all grades of hemorrhoids combined. When outcome data were stratified by grade of hemorrhoid, results for response to therapy of Grades 1 to 2 and for Grade 3 hemorrhoids were assessed. Grade 4 hemorrhoids were assessed in only seven patients in all trials combined and, thus, were not included in the analysis. Odds ratios, combined odds ratios, and probability (*P*) values for each of the comparisons and outcome measures available are listed in Tables 3 to 7.

Hemorrhoidectomy was found to be significantly more effective than MDA overall and for Grade 3 hemorrhoids ($P = 0.0017$), with less need for further therapy ($P = 0.034$), no significant difference in complications (although there was a trend toward an increased risk of incontinence following MDA with $P = 0.07$), but significantly more pain following SH ($P < 0.0001$). Overall, patients undergoing hemorrhoidectomy also had a significantly better response to treatment than did patients treated with rubber band ligation ($P = 0.001$), although this was at a cost of a significantly greater risk of complications ($P = 0.02$) and pain ($P < 0.0001$). When stratified by grade, only Grade 3 hemorrhoids were amenable to comparison between RBL and SH. For Grade 3 hemorrhoids alone, no difference was shown. RBL was shown to be significantly better than IS in response to treatment ($P = 0.005$). This difference was shown for both Grades 1 and 2 ($P = 0.007$) hemorrhoids or Grade 3 hemorrhoids ($P = 0.042$), with no significant difference in the complication rate. Patients treated with RBL were less likely to require further therapy than those treated with either sclerotherapy ($P = 0.031$) or infrared coagulation ($P = 0.0014$), although pain was significantly more likely to occur following rubber band ligation (IS, $P = 0.03$; IRC, $P < 0.0001$). No difference was found between sclerotherapy or infrared photocoagulation for any of the outcome measures.

DISCUSSION

The virtue of meta-analysis is its ability to provide a statistical consensus when published results have been conflicting or nondefinitive. A caveat to the use of meta-analysis is that "as with any research study, a number of methodologic decisions must be made when undertaking a systematic review, and there are potential threats to validity associated with each decision. These include: how studies are identified and selected for inclusion, how their quality is assessed . . . and how results are combined and interpreted" (Oxman A, unpublished data) Thus, the reader must be satisfied that the methodology of the meta-analysis is sound before accepting the conclusions.

Bias in selection of papers for inclusion in a review may affect results. An attempt was made to minimize this bias by first ensuring as complete a retrieval as possible with a broad-search strategy and by having relatively liberal inclusion criteria. Inclusion or exclusion established by consensus of two reviewers blinded to results also helped to minimize selection bias. Finally, all randomized trials identified in the search of the literature, along with the exclusion criteria, are listed to facilitate the reader in evaluating the appropriateness of the trials included and excluded. Publication bias did not seem to be a major concern because most trials in this analysis were not positive; thus, a treatment effect did not appear to be a major determinant of publication.

Quality of the studies included is another potential problem in the evaluation of a meta-analysis. Studies of high quality are more likely to yield truthful results than studies with less methodologic rigor; thus, combining them with equal weight may be problematic. However, it may also be difficult to assign weighting systems for studies of varying quality because any system used is somewhat arbitrary.[43] As there was little variation in the quality of studies included, this difficulty was avoided. Of more concern was that the overall quality of studies was not high, decreasing the strength of the conclusions of this meta-analysis.

Another concern in the use of meta-analysis is the question of which studies should be combined to avoid pooling together of apples and oranges.[6] In this meta-analysis the criteria for entry into each of the studies were similar, although grade of hemorrhoid treated varied among studies. This was controlled for by stratifying the results by grade when possible. The patient populations and treatment methodology of each of the modes of therapy used were very similar. Unfortunately, however, the main outcome measure, response to therapy, had very low objectivity as it was assessed by patients' assessment of therapy on a 3-point to 4-point categoric scale in most trials. This low objectivity may have lead to the combination of heterogeneous data if patients were responding to the categories differently in the various trials. In view of the concern with both the quality of the studies included and the possibility of heterogeneity of the outcome measure, the confidence intervals of the combined odds ratios may be artificially narrow.

The method of combining trials is another source of variation in development of a meta-analysis. A random effects model is more conservative in its estimate of the confidence interval; however, this model is based on the assumption that there is a hypothetical universe of trials, requiring a between-study variability component.[44] This may lead to a conclusion of no effect when one exists and may give undue weight to small studies.[6] For these reasons, the fixed effect model was used in this meta-analysis.

Findings of this meta-analysis are that, for Grade 3 hemorrhoids, the decline in use of MDA appears to have been justified. Patients have lower rates of response, are more likely to require further therapy, and have a trend toward a higher incidence of incontinence after MDA than following hemorrhoidectomy. Current practice parameters of the American Society of Colon and Rectal Surgeons[45] agree that the use of MDA should be avoided. No difference was shown in response rates between hemorrhoidectomy and RBL for Grade 3 hemorrhoids, but as the numbers of patients in the two trials compared were relatively small and a difference favoring hemorrhoidectomy was shown for all hemorrhoids, this likely represents a Type II or beta error.[1] However, RBL ligation is an outpatient procedure that does not require time off from work, has good response rates, and has significantly fewer complications with less pain than associated with hemorrhoidectomy. Thus, it seems justifiable to use RBL as a first-line treatment for Grade 3 prolapsing hemorrhoids, reserving hemorrhoidectomy for patients whose symptoms are not relieved. RBL was shown to be superior to sclerotherapy for Grade 3 hemorrhoids with respect to response to therapy. IRC was not evaluated for Grade 3 hemorrhoids in any of the trials; however, in view of the finding that patients undergoing IRC are more likely to require further therapy than those having RBL for early hemorrhoids, it seems reasonable to assume that RBL would show greater efficacy in treatment of more advanced disease.

For Grades 1 to 2 hemorrhoids, RBL appears to be the therapy of choice. Patients undergoing RBL showed a significantly better response to therapy than those treated with IS and a significantly decreased need for further therapy than patients having either IS or IRC. Although RBL was more painful than other outpatient modalities, complication rates were similar. Because of insufficient numbers of studies, bipolar therapy could not be directly assessed in this meta-analysis. However, the mode of action of bipolar therapy is similar to that of IRC, with each applying a depth of coagulation of 3 mm.[13] It seems likely that results of bipolar therapy would be similar to those of IRC in the long term.

Johanson and Rimm[46] reported a meta-analysis of outpatient hemorrhoid therapy for Grades 1 to 2 hemorrhoids, comparing RBL to IRC and to IS. The findings of their analysis were similar, although the present meta-analysis evaluated a broader range of treatment modalities and grade of hemorrhoids, including more studies. The other difference was the use of a random effects model by Johanson and Rimm compared with the fixed effects model we used. Despite differences in the methods of the two meta-analyses, the results of the analyses were similar for the methods and grade of hemorrhoids compared in both studies. Johanson and Rimm did not recommend RBL as the preferred initial treatment for Grade 1 to 2 hemorrhoids because of the risk for pelvic cellulitis following this procedure.[47–49] This was not a reported complication in any of the studies included in the meta-analysis. Despite widespread use of banding, this complication is exceedingly rare. To minimize the risk, before banding care should be taken to ensure that patients are not immunocompromised, and patients should be warned of symptoms of pelvic infection to facilitate early recognition and treatment of this rare complication.

A disappointing finding of this meta-analysis was the relatively low number of randomized trials evaluating hemorrhoid therapy. Symptomatic hemorrhoids affect 4.4 percent of the population, and of these, approximately one-third present to physicians for evaluation.[50] Therefore, the prevalence of this disease is high with good opportunity for large, well-designed, randomized trials to settle any uncertainty.

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