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Enucleation versus hepatectomy for giant hepatic haemangiomas: a meta-analysis

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ABSTRACT

INTRODUCTION Hepatic haemangiomas are the most common benign liver tumours. They can be treated with surgical resection such as enucleation or hepatectomy if necessary. However, controversy remains over the clinical outcome and safety of these two methods. In this study, we performed a comprehensive meta-analysis to compare the efficacy of liver resection with enucleation for giant haemangiomas.

METHODS The online databases PubMed, Embase and CNKI (China National Knowledge Infrastructure) were searched for relevant original articles. We compared operation time, blood loss, transfusion requirements, inflow occlusion time and postoperative complications between enucleation and hepatectomy.

RESULTS Seven controlled clinical trials met the predefined inclusion criteria. Analysis indicated that the enucleation group had significantly shorter operation time (weighted mean difference, WMD –28.22, 95% confidence interval, CI, –54.82 to –1.62), less blood loss (WMD –395.92, 95% CI –521.25 to –270.58) and fewer complications (odds ratio, OR, 0.47, 95 % CI 0.34 to 0.65). There were no significant differences between enucleation and hepatectomy with regard to transfusion requirements (OR 0.61, 95% CI 0.22 to 1.68) and inflow occlusion time (WMD 7.91, 95% CI –5.62 to 21.44).

CONCLUSIONS Enucleation has advantages over hepatectomy in relation to operation time, blood loss and complications. Enucleation is a safe and effective treatment for giant hepatic haemangioma.

KEYWORDS

Haemangioma – Hepatectomy – Enucleation – Liver Resection – Meta-Analysis

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Introduction

Haemangiomas are the most common benign hepatic tumours, and the prevalence ranges from 3–20% in autopsy series. They are usually asymptomatic with normal liver function and do not require intervention. The diagnosis is most commonly made by ultrasound, computed tomography (CT) or during laparotomy for other intra-abdominal disease.[1] Larger tumours (often defined in the literature as 'giant haemangiomas' when the size exceeds 4 cm)[2] are frequently associated with symptoms including abdominal discomfort and life-threatening complications.

Many treatment options are available for hepatic haemangiomas, such as medical therapies, arterial ligation, transcatheter arterial embolisation (TAE), radiofrequency ablation, liver transplantation and surgical resection.[3,4] Surgical resection, which includes enucleation and hepatectomy, provides the most effective method of treatment for patients with symptomatic haemangiomas.[5] Current indications for surgical resection of haemangioma include rapid enlargement, abdominal pain, potential rupture and uncertainty of diagnosis.

Enucleation is a new technique relative to conventional hepatectomy, which is performed by dissecting the tumour from the surrounding liver parenchyma along the plane of the tumour capsule. A series of prior studies reported conflicting evaluation of surgical outcomes between enucleation and hepatectomy. We undertook the present meta-analysis to compare the efficacy of liver resection with enucleation for giant haemangiomas.

Materials and Methods

Search strategy and study selection

The online databases PubMed, Embase and CNKI (China National Knowledge Infrastructure) were searched to identify eligible studies published from 1 January 1988 to 31 August 2016. The search terms were 'hemangioma' AND 'enucleation' AND ('hepatectomy' OR 'liver resection'). Some studies were also identified by the references cited in selected articles, which were then searched manually.

Selection criteria

Studies were included in the current meta-analysis if they met the following criteria: randomised controlled trials, non-randomised controlled trials, retrospective clinical or cohort studies; comparison between enucleation and hepatectomy; full text available. Age and sex of the patient and tumour size were ignored. Cases were excluded from this study if they were described in case reports, review articles, or were only reported as abstracts or with incomplete data. They were also excluded if the comparison was with laparoscopic hepatectomy, if there was no comparison between enucleation and hepatectomy, or if other benign liver lesions, not haemangiomas, were described. If studies had overlapping subjects, only the study with the largest sample size was included in the final analysis.

Data extraction and quality assessment of studies

Two reviewers (Cheng and Qi) independently reviewed the articles and extracted the following data from all eligible publications: first author, year of publication, country, number of patients, tumour size, operation time, amount of blood loss, transfusion requirements, inflow occlusion time and postoperative complications. Discrepancies between two reviewers were resolved by discussion or by a third person (Tian).

The methodological quality of the studies was evaluated independently by two reviewers using the Newcastle–Ottawa scale (NOS)[6] to assess the quality of non-randomised studies. The maximal score of NOS is nine stars: four stars for the selection process, two stars for comparability and three stars for exposure/outcome, with a score five or more indicating high quality.

Data analysis

Meta-analysis was performed with Review Manager Version 5.0 software (Cochrane Collaboration, Oxford, UK). The estimated effect measures were odds ratio for dichotomous data and weighted mean difference for continuous data; both reported with 95% confidence intervals. All results were assessed for clinical and statistical heterogeneity. Heterogeneity was evaluated using the χ^2 test with significance set at $P \geq 0.10$ and I^2 statistics were used for the evaluation of statistical heterogeneity ($I^2 \geq 50\%$ indicating presence of heterogeneity).[7] To pool all available data, continuous outcomes from clinical trials reported with median, range and sample size values were converted to mean and standard deviation values using the statistical method developed by Hozo et al.[8] We used a fixed effects model to synthesise data when heterogeneity was absent; otherwise a random effects model was used. Subgroup analysis was conducted when clinical or methodological heterogeneity might exist. Data were presented as forest plots and the funnel plot was used to assess publication bias. $P < 0.05$ was considered to be statistically significant.

Results

We identified 56 relevant studies after viewing the titles and abstracts; 29 studies met the exclusion criteria, there were 3 reviews, 3 case reports, 4 duplicates and 19 irrelevant studies. The remaining 27 studies were retrieved for full-text review. Finally, 7 studies involving 913 patients were included in the meta-analysis.[9–15]

All included studies were non-randomised controlled trials. Three were from the United States, one was from Turkey, one from India, one from Italy and one from China. A total of 477 patients underwent enucleation and 436 underwent hepatectomy. The average tumour size was not significantly different between enucleation groups and hepatectomy groups in each study. The main characteristics of the studies are summarised in Table 1.

The methodological quality assessment for the included studies is showed in Table 2. The seven studies were of a similar high quality with NOS scores ranging from 5 to 8 stars.

Data on operation time from six trials are included in the analysis. There was no obvious heterogeneity among the trials (χ^2 15.50, 5 degrees of freedom, $P < 0.10$; I^2 52%). We performed a random effects model and the data indicated that the operation time of enucleation was significantly shorter than hepatectomy (WMD –28.22, 95% CI –54.82 to –1.62; $P < 0.05$).

Blood loss data from five trials are included in the analysis. There was moderate heterogeneity among the trials (χ^2 11.37, 4 degrees of freedom, $P < 0.10$; I^2 65%). We performed a random effects model and the data indicated that the amount of blood loss from enucleation was significantly less than hepatectomy (WMD –395.92, 95% CI –521.25 to –270.58; $P < 0.05$).

Three trials reported the number of patients who needed transfusion in the two groups. The total transfusion rate of 14.3% (7/49) was identified in the enucleation group and 19.0% (12/63) in the hepatectomy group. A fixed effects model indicated no significant difference in transfusion rate between the two groups (OR 0.61, 95% CI 0.22 to 1.68; I^2 20%, $P < 0.05$).

Inflow occlusion time data from three trials are included in the analysis. A random effects model showed that the inflow occlusion time between the two groups was not significantly different (WMD .91, 95% CI –3.62 to 21.44; I^2 = 51%, $P < 0.05$).

All trials provided information about postoperative complications, including bile leakage, ileus, gastrointestinal bleeding and wound infection. The pooled incidence of complications was 17.0% (81/477) in the enucleation group and 28.4% (124/436) in the hepatectomy group. A fixed effects model indicated that the incidence of complications in enucleation group was significantly less than that in the hepatectomy group (OR 0.47, 95% CI 0.34 to 0.65; I^2 = 1%, $P < 0.01$).

When the number of studies included was greater than five, funnel plots could be carried out. The indicators, which

Table 1 Characteristics of 56 studies included in meta-analysis

Study	Patients (*n*)	Tumour size (cm)		Operation time (minutes)		Blood loss (ml)		Patients needing transfusion (*n*)	Inflow occlusion time (minutes)		Postoperative complications (*n*)
		Mean	SD	Mean	SD	Mean	SD		Mean	SD	
Kuo et al, 1994, US											
Enucleation	10	7.6	1.3	132	18	400	129	1	NR	NR	0
Hepatectomy	10	8.4	1.2	144	12	742	116	3	NR	NR	2
Gedaly et al, 1999, US											
Enucleation	23	6	3.7	204	72	923	1033	NR	14	18	8
Hepatectomy	5	8.6	5.4	258	90	2080	1139	NR	19	20	4
Lerner et al, 2004, US											
Enucleation	27	10.1	5.3	174	72	NR	NR	4	23	12	3
Hepatectomy	25	11.6	4.3	198	65	NR	NR	7	15	9	11
Hamaloglu et al, 2005, Turkey											
Enucleation	10	7.8	0.7	110	27	150	189	NR	NR	NR	1
Hepatectomy	12	8.1	0.8	190	95	375	339	NR	NR	NR	2
Singh et al, 2007, India											
Enucleation	9	8.9	3.3	175	35	400	116	NR	NR	NR	0
Hepatectomy	12	10	6.2	223	78	1329	1485	NR	NR	NR	5
Giuliante et al, 2011, Italy											
Enucleation	12	12.3	12.9	323	138	NR	NR	2	79	50	1
Hepatectomy	28	11.8	9.2	260	140	NR	NR	4	48	26	3
Qiu et al, 2015, China											
Enucleation	386	6.7	2.2	NR	NR	400	75	NR	NR	NR	68
Hepatectomy	344	6.9	2.3	NR	NR	860	158	NR	NR	NR	97

NR, not reported

were based on operation time and complications, revealed the existence of some degree of publication bias.

Discussion

Enucleation and hepatectomy are two surgical methods of resection for giant hepatic haemangioma, both of which have low mortality rates. The method selected depends on the preference of the individual surgeon. Resection of a hepatic haemangioma was first reported by Hermann Pfannenstiel in 1898 and for some time remained the only consistently effective method of treatment.[16] In 1988, Alper et al.[17] described a new technique for haemangioma enucleation by means of dissection in a fibrous cleavage plane between the capsule of the haemangioma and the surrounding normal liver tissue. Some authors advocate traditional liver resection,[18,19] because in cases of large and deep haemangiomas in proximity to vascular structures, typical liver resection is a safe operation with lower mortality and blood loss. Others, however, advocate enucleation,[20] believing that this technique avoids the need to resect normal liver parenchyma and minimises damage to blood vessels and bile ducts. Our meta-analysis indicated that operation time was shorter, there was less blood loss and complications were fewer in number in the enucleation group, and that the differences were statistically significant.

Massive bleeding can be a serious problem during surgical resection for giant hepatic haemangioma. Severe blood loss is a major cause of complications. In our experience, hepatectomy damages blood vessels and bile ducts more frequently, and the surgeon usually spends more time in ligation and haemostasis. Enucleation, which is performed along the envelope of haemangioma, retains regular liver cross-section and avoids significant blood vessels and bile ducts, resulting in less blood loss and bile leakage. The large amount of blood loss in the hepatectomy group might

Table 2 Quality assessment of nonrandomised controlled trials included in the meta-analysis, based on the Newcastle–Ottawa scale

Study (year)	Stars (*n*)				Study quality
	Selection	Comparability	Outcome	Total	
Kuo et al (1994)	3	2	2	7	High
Gedaly et al (1999)	2	2	2	6	High
Lerner et al (2004)	2	2	2	6	High
Hamaloglu et al (2005)	2	1	2	5	High
Singh et al (2007)	1	2	2	5	High
Giuliante et al (2011)	3	2	2	7	High
Qiu et al (2015)	3	2	3	8	High

explain why the operation time was longer and the incidence of complications higher than in the enucleation group.

A few studies reported other effective treatments for giant haemangiomas. Hepatic haemangioma in the left liver lobe or ventral segments can also be resected by laparoscopic surgery with many advantages, such as a smaller wound and a faster return to full activity. Some case reports have described a laparoscopic approach to liver haemangioma.[21]

Laparoscopic enucleation of haemangiomas will remain challenging because of the risk of bleeding and is preferably performed by surgeons with rich experience. Symptomatic giant liver haemangiomas can be managed successfully by TAE with a satisfactory decrease in symptoms and tumour volume.[22] Some authors have reported cases of huge haemangiomas that were successfully resected following effective TAE.[23] The results indicate the importance of preoperative management to reduce tumour size by TAE.

This study had a number of limitations that should be acknowledged. First, all the trials included were nonrandomised controlled trials, and there were small numbers of patients in each trial, so the evidence from these studies is not of the highest quality. Second, there was a lack of available data on postoperative outcome. Third, different lesions location in each group determined the different degree of operation difficulty. The heterogeneity of the patients included may have influenced the conclusions. Considering our limitations and the heterogeneity among our chosen studies, large and well-designed prospective studies are needed to determine the future curative effect of enucleation.

Conclusions

The meta-analysis revealed that hepatic enucleation has advantages over hepatectomy in relation to operation time, blood loss and complications, but the aspects of transfusion requirements and inflow occlusion time are not significantly different between the two surgical methods. Therefore, we recommend enucleation, when feasible, as the preferred surgical technique of choice for giant hepatic haemangioma.

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