Title:

Treatment of intrahepatic congenital portosystemic shunts in dogs: a systematic review

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Treatment of intrahepatic congenital portosystemic shunts in dogs: a systematic review

Objectives: To establish the evidence base for the treatment of intrahepatic congenital portosystemic shunts (CPSS) in dogs.

Methods: A systematic review of the literature relating to the treatment of intrahepatic CPSS in dogs was performed. Studies were filtered for evidence to answer the question “Which of the treatment options for intrahepatic CPSS in dogs offers the best short and long term outcome?” Studies were assigned a level of evidence based on a system published by the Oxford Centre for Evidence-Based Medicine.

Results: Thirty-two studies were included in the review. Twenty-six provided level 4 evidence and six provided level 5 evidence. There were no level 1, 2 or 3 studies. One study compared surgical treatment with medical management and one study compared suture ligation with ameroid constrictor placement. The remaining studies were case series describing the outcome for one treatment only. There was considerable variation between studies in terms of the method and timings of assessment of short and long-term outcome, making direct comparison challenging.

Clinical Significance: The evidence for the treatment of intrahepatic CPSS in dogs is weak, with only two studies directly comparing treatments. There is a lack of evidence of short and long-term outcomes on which to base firm clinical decisions. Further research should aim to produce a consistent method of outcome assessment and compare different treatment options.
Introduction

A variety of treatments have been recommended for dogs with intrahepatic congenital portosystemic shunts (CPSS) (White et al. 1998, Hunt et al. 2004, Adin et al. 2006, Mehl et al. 2007, Berent and Tobias 2009, Weisse et al. 2014). Surgical intervention to attenuate the abnormal vessel either acutely or gradually is recommended for most dogs (Berent and Tobias 2009, Greenhalgh et al. 2014). By improving or restoring normal portal blood flow this typically results in resolution of clinical signs and improvement in biochemical parameters (Breznock et al. 1983, White et al. 1998).

However, incomplete treatment because of persistent shunting or the development of multiple acquired shunts can result in ongoing or recurrent clinical signs (White et al. 1998, Kummeling et al. 2004). Long-term medical management can also be used in animals where surgery is not available or is declined by the owner (Watson and Herrtage 1998, Greenhalgh et al. 2014).

For many years, surgical attenuation of intrahepatic CPSS was the recommended treatment either using suture ligation, an ameroid constrictor, a cellophane band or a hydraulic occluder (Komtebedde et al. 1991, White et al. 1998, Papazoglou et al. 2002, Hunt et al. 2004, Adin et al. 2006, Mehl et al. 2007). However, it is recognised that intrahepatic CPSS can be more challenging to treat surgically than extrahepatic CPSS due to the location of the abnormal vessel within the liver parenchyma. Different strategies have been used to access the CPSS surgically to allow attenuation and the method employed is dependent on the morphology of the CPSS. Extravascular surgery involves dissection of the CPSS itself, the draining hepatic vein or the portal vein branch supplying it. Reports have also described the use of intravascular techniques to allow
attenuation of some IHCPSS, which is technically more demanding (Breznock et al. 1983, Hunt et al. 1996, White et al. 1998). Concern over peri-operative complications and mortality has prompted the development of a minimally invasive treatment for intrahepatic CPSS (Bussadori et al. 2008, Weisse et al. 2014). Endovascular coil embolization with interventional radiology has been recommended to reduce complications and mortality associated with traditional surgical techniques (Weisse et al. 2014). Whilst many authorities recommend certain treatments over others there is a lack of a consensus on which is best. Establishing the evidence base for the treatment of dogs with intrahepatic CPSS is very important to allow owners and veterinary surgeons to make informed decisions.

A previous review assessed the evidence base for the surgical treatment of extrahepatic CPSS in dogs (Tivers et al. 2012). Published studies on CPSS in dogs were graded on the level of evidence that they provided to answer this question. This review found that the evidence base for the treatment of extrahepatic CPSS in dogs was weak, meaning that it was not possible to make firm recommendations.

We therefore undertook a systematic review of the current literature to determine the evidence base for the treatment of intrahepatic CPSS in dogs. The aim of the study was to assess the evidence base with a view to identifying whether one treatment could be recommended over another based on short and / or long-term outcome.

Materials and Methods
The following question was formulated to establish the evidence base for the treatment of intrahepatic CPSS in dogs: “Which of the treatment options for intrahepatic CPSS in dogs offers the best short and long term outcome?” An online bibliographic search was performed in November 2016 for studies relating to the treatment of intrahepatic CPSS in dogs. The search utilised the PubMed (http://www.pubmed.gov/) and ISI Web of Science (http://wok.mimas.ac.uk/) databases. Databases were searched using the following terms: (portosystemic shunt OR portocaval shunt OR portovascular anomaly OR portosystemic communication OR intrahepatic vascular anomaly OR intrahepatic shunt) AND (dog OR canine OR canid) AND (treatment OR outcome OR mortality OR morbidity OR complications). Following this process, the databases were also searched using the following terms: (portosystemic shunt(s) OR portocaval shunt(s)) AND dog. This was to ensure that any studies that were not captured in the original, more specific search, were included.

Analysis was restricted to the English language veterinary literature reporting information on the treatment of intrahepatic CPSS in dogs. The abstracts were reviewed for relevance to the question. Studies were excluded if they were experimental, described only acquired PSS or extrahepatic CPSS, were case reports or small case series (less than five dogs) or did not provide any detail regarding outcome (e.g. studies describing diagnostic tests, etc.).

Studies meeting these criteria were reviewed by the primary author and were assigned a level of evidence based on the system published by the Oxford Centre for Evidence-Based Medicine (OCEBM Levels of Evidence Working Group 2017) (Table 1).
The following data was recorded from each study: the type of study described (i.e. case series, cohort study, etc.); the number of dogs included; the treatment used; the short-term outcome in terms of mortality rate; the long-term outcome including duration of follow-up and method of assessment. It was anticipated that the type of outcomes reported, particularly for long-term outcome, would vary between studies. Therefore, the method of outcome assessment, the timing and the result were also recorded.

Results

Thirty-two studies were identified as providing relevant information for answering the question (Table 2). Twenty-six were classified as level 4 and the remaining six were classified as level 5. There were no level 1, 2 or 3 studies.

Direct comparison of different treatments

Three studies were identified that compared the outcome of two different treatments (Mehl et al. 2007, Greenhalgh et al. 2010, Greenhalgh et al. 2014). Two of these studies described a prospective comparison of medical and surgical management in the same cohort of dogs so the more recent paper was chosen to represent this dataset (Greenhalgh et al. 2010, Greenhalgh et al. 2014). This was a prospective cohort study that directly compared the short and long-term outcome for 27 dogs treated with medical management and 97 dogs treated with surgical attenuation (Greenhalgh et al. 2014). The study included 110 dogs with extrahepatic CPSS and 14 dogs with intrahepatic CPSS. Eight of the intrahepatic CPSS dogs had surgery and six were treated medically. Long-term follow-up was obtained by owner questionnaires and telephone calls with owners and the referring veterinary surgeons. Twenty-four out of 27 dogs
(89%) treated medically died or were euthanised during the follow up period. The median survival time was 836 days. Twenty-one out of 97 dogs (22%) treated surgically died or were euthanised during the follow-up period. This included five dogs (5.2%) that died in the peri-operative period (≤7 days after surgery), including one dog that died following a second surgery. Seven dogs (7.2%) in the surgery group were lost to follow-up. It was not possible to estimate median survival for the surgically treated dogs due to the large number that were still alive at follow-up. The survival rate for surgically treated dogs was statistically significantly greater than that of those managed medically. There was no significant effect of shunt type (extrahepatic versus intrahepatic) on survival. The frequency of ongoing clinical signs was statistically significantly better for surgically treated dogs (completed questionnaires from 46/75 dogs alive) compared with medically treated dogs (completed questionnaires from 6/9 dogs alive) 4-7 years after study entry.

There was a single retrospective study comparing the outcome for dogs with left divisional intrahepatic CPSS treated with suture ligation and ameroid constrictors (Mehl et al. 2007). This study reported the short and long-term outcomes for 17 dogs treated with partial ligation with 11 dogs treated with ameroid constrictors. Two dogs in the partial ligation group (11.8%) and one dog in the ameroid constrictor group (9.1%) suffered postoperative complications. Overall one dog died in the partial ligation group (5.9%) due to a severe coagulopathy and one dog died in the ameroid constrictor group (9.1%) due to post-operative seizures. There was no significant difference in the surgical morbidity or mortality between the two techniques. A proportion of the dogs had portal scintigraphy performed at 6-10 weeks' post-surgery. Persistent shunting was
identified in 7/8 dogs in the partial ligation group (87.5%) and in 3/7 dogs in the ameroid constrictor group (42.9%). There was no statistically significant difference in the proportion of dogs with persistent shunting on scintigraphy between the two groups. Long-term clinical outcome was assessed via a telephone questionnaire with the owner or referring veterinary surgeon. An excellent outcome was defined as “dogs that were free of any clinical signs and not on any special dietary requirements or medications”, a good outcome included “dogs that were perceived to be clinically normal according to the owners, and were maintained on low protein diets and/or medical therapy” and a poor outcome included “dogs that showed no improvement after surgery and remained clinical for a PSS or had worsening clinical signs” (Mehl et al. 2007). Outcome was obtained for 13 dogs in the partial ligation group at a median of 50 months (range 6-122) post-surgery and for 10 dogs in the ameroid constrictor group at a median of 28.5 months (range 14-54) post-surgery. In the partial ligation group outcome was excellent in 12/13 (92%) and good in 1/13 (8%). The dog with a good outcome had persistent flow through the shunt. A second surgery was performed and complete attenuation was achieved, resulting in an excellent outcome for this dog. In the ameroid constrictor group the outcome was excellent in 2/10 (20%), good in 5/10 (50%) and poor in 3/10 (30%). The three dogs with a poor outcome had all been euthanised due to signs of hepatic insufficiency at 14, 19 and 27 months post-surgery. The long-term outcome, in terms of grade, was significantly better in dogs treated with suture ligation compared with ameroid constrictors.

Case series reporting the outcome for one treatment
There were 21 studies that were case series reporting the short and/or long-term outcome for a single treatment for intrahepatic CPSS in dogs. Two of these were prospective studies and the remainder were retrospective. Sixteen studies described various types of surgical treatment and these are summarised in Table 3. Four studies described endovascular coil embolization and these are summarised in Table 4. One study described medical management and this is summarised in Table 5. An additional eight studies were identified that were level 5 evidence (Table 2). Whilst they contained some information on outcome this was either insufficient to justify their inclusion or it was not possible to differentiate the outcome data for dogs with intrahepatic CPSS from those with extrahepatic CPSS. A summary of short and long-term outcome for different surgical procedures (including endovascular coil embolization) is presented in Table 6. For suture ligation and endovascular coil embolization this included the larger studies only.

Discussion

This systematic review of the literature regarding the treatment of intrahepatic CPSS in dogs reveals that the evidence base for recommending treatments is very weak. When attempting to determine the most effective treatment or intervention for a given disease or condition the decision should ideally be based on the most reliable evidence available. There are several systems available that can be used to rank evidence (Howick et al. 2017). A previous review of the evidence base for the treatment of extrahepatic CPSS in dogs used a modification of an existing grading system (Tivers et al. 2012). This system was published by the Oxford Centre for Evidence-Based Medicine but has subsequently been revised (OCEBM Levels of Evidence Working Group 2017).
The revised version was designed so that the structure reflects clinical decision making and is simpler, refraining from making definitive recommendations (Howick et al. 2017). Importantly, unlike other systems, it is suitable for use when no systematic reviews are available (Howick et al. 2017). The current review used the revised version as we believed that these modifications made it more suitable for application to the veterinary literature.

It is generally accepted that systematic reviews of randomised controlled trials (RCTs) provide the most reliable evidence. Unfortunately, RCTs are very uncommon in the veterinary literature. Perhaps unsurprisingly, the current review did not identify any level 1, 2 or 3 studies reporting the outcome for dogs with intrahepatic CPSS. Most studies were level 4 case series describing the outcome for a single treatment. Therefore, the evidence that is available to make decisions on which treatment to use is very limited. Several studies were level 5, providing minimal evidence to answer the question. These studies either did not provide any useful information regarding outcome or provided combined outcome data for intrahepatic and extrahepatic CPSS and it was not possible to separate these out. This is not intended as a criticism of these studies, rather that they did not provide good evidence for the question asked in the current review.

We did not attempt to categorise the level 4 studies further, although Table 2 does show the types of study represented. There was one prospective cohort study that compared the outcome of surgical treatment with medical treatment (Greenhalgh et al. 2014). The results of this study strongly support the use of surgical treatment over medical
management for most dogs. However, it should be recognised that although this study was prospective, it was not randomised and there may have been significant selection bias affecting the distribution of dogs into the two treatment groups. In addition, the study included dogs treated with a variety of techniques and it is therefore difficult to determine the effect of a given surgery. Importantly, the study included dogs with both intrahepatic CPSS and extrahepatic CPSS and it was not possible to separate the data for the two groups in detail (although morphology did not influence survival). There was also a relatively small number of dogs with intrahepatic CPSS, with eight treated surgically and six managed medically.

A single study retrospectively compared dogs treated with partial suture ligation with those treated with ameroid constrictor placement (Mehl et al. 2007). This study found that there was no difference in peri-operative complications and mortality but that the long-term outcome was significantly better for those dogs treated with suture ligation. This study had good long-term follow-up but there were relatively small numbers of dogs in both groups (17 suture ligation and 11 ameroid constrictor). It is noteworthy that this report only described dogs with one type of intrahepatic CPSS (left divisional). It is therefore unclear if these results can be extrapolated to other morphologies of intrahepatic CPSS.

The remaining studies were case series describing the outcome for one type of treatment, including surgical techniques, endovascular coil embolization and medical management (summarised in Tables 3, 4 and 5). However, several studies reported more than one surgical technique, which makes drawing firm conclusions on individual
treatments difficult. Some studies described dogs that had suture ligation, intravascular
attenuation and/or the placement of mattress sutures or hemoclips (Breznock et al.
1983, Komtebedde et al. 1991, White et al. 1998). It is arguable that these can be
considered as one group as they are techniques providing acute attenuation and the
choice is dictated largely by the morphology of the shunt. However, it is well recognised
that intravascular techniques are more complex and technically demanding and their
use in some case series and not in others may have skewed the results. Two other
studies report dogs treated with a variety of techniques including both acute and
gradual attenuation methods and this makes interpretation of these results difficult

Overall, the studies identified in this review provide a considerable amount of
information but it is difficult to directly compare them due to the wide variation in the
way that outcome has been measured and reported. Short-term outcome can be
considered easier to quantify, particularly in terms of morbidity and mortality.
However, studies vary in the type of complications that are reported and the time frame
in terms of intra, peri and post-operative periods. We did not record complication rates
for most studies due this variability. Mortality is a more absolute variable, although the
time frame for peri or post-operative mortality can range from the duration of
hospitalisation to 30 days’ post-surgery. Some small studies report a mortality rate of
0% but this is likely to reflect the number of dogs included rather than the absolute
success of the procedure. A summary of the short-term outcome according to surgical
procedure is presented in Table 6. This is particularly limited by the small numbers of
dogs treated with ameroid constrictors and cellophane bands, making direct
comparison from this table challenging. Surgical attenuation of intrahepatic CPSS has been associated with a relatively high rate of peri-operative complications and death. Two studies, which are commonly referenced, were not included in the Table 6, one due to relatively small numbers (Komtebedde et al. 1991) and one due to the inclusion of several different surgical techniques (Papazoglou et al. 2002). These studies reported complication rates of 77% and 47% respectively, which were greater than those included in Table 6. These studies also reported a mortality rate of 23.1% and 12.5% respectively, both within the range reported in Table 6. Endovascular coil embolization is recommended as a minimally invasive treatment for intrahepatic CPSS to reduce the morbidity and mortality associated with open surgery. A large study of 95 dogs treated with endovascular coil embolization reported a post-operative complication rate of 18.9% and a mortality of 5.3%. The complication rate for this group of dogs is somewhat unclear as both intra-operative and post-operative complications are reported separately and complications are reported for 111 procedures, including repeat procedures in several dogs and five animals that did not have coils placed due to evidence of portal hypertension.

The long-term outcome of intrahepatic CPSS treatment is more challenging to assess than the short-term outcome. A variety of outcome measures have been used, including clinical assessment, owner assessment, serum bile acids or ammonia tolerance testing, ultrasound and scintigraphy (White et al. 1998, Hunt et al. 2004, Kummeling et al. 2004, Adin et al. 2006, Mehl et al. 2007, Weisse et al. 2014). However, it is unclear which of these represent the most appropriate or reliable assessment. Table 6 also summarises the long-term outcome of the different treatments, showing that all have relatively
similar results. The wide variation in both the method of long term follow up and the
definition of an ‘excellent’ or ‘good’ outcome make direct comparison for the different
techniques challenging. If we consider a poor outcome then we can summarise the data
as follows. For dogs treated with suture ligation 0-16.2% of dogs had a poor outcome
with recurrent or persistent signs and / or shunting at an average of 16-50 months’
post-surgery (including those that had repeat surgery) (White et al. 1998, Kummeling et
al. 2004, Mehl et al. 2007). For dogs treated with ameroid constrictors 12.5-30% had a
poor outcome, with euthanasia due to persistence or recurrent clinical sings at an
average of 28.5-38.3 months’ post-surgery (Bright et al. 2006, Mehl et al. 2007). This is
compared to coil embolization where 19% of dogs had a poor outcome with continued
or worsening clinical signs despite medical management or surgical related death at a
median of 32.1 months post-treatment (Weisse et al. 2014). Similarly, it should be
recognised that this information is based on a small number of dogs treated with
ameroid constrictors and a single study, albeit with a large number of dogs, treated with
coil embolization.

This review highlights the relative lack of information on long-term outcome for
intrahepatic CPSS treatment. Further information is needed to determine which
treatment gives the best long-term outcome. Currently, the ideal end-point for CPSS
occlusion is unclear. It is unknown whether the aim of surgery should be to achieve full
attenuation in every animal or whether some degree of persistent shunting is
acceptable. This should be addressed so that the most appropriate treatment can be
recommended to achieve a good long-term outcome. Further comparative clinical
studies are essential to determine the precise pros and cons of different treatment
options. Importantly, we need studies that compare both the short-term morbidity and mortality and the long-term outcome in terms of quality of life. Ideally studies would compare different types of surgical attenuation with each other and coil embolization based on random allocation. However, different shunt morphology may also influence the results of different surgical techniques and therefore, it may be sensible to compare treatments for each broad shunt morphology. There is a need for studies to include larger numbers of dogs to increase their reliability. This may be best achieved through collaboration between several centres.

There are other factors besides risk of morbidity and mortality that will influence decision-making, which were not assessed as part of the current review. These include availability of equipment and expertise, financial considerations and client and surgeon preference. Importantly there may be factors relating to the individual dog that may influence choice of treatment, particularly the morphology of the CPSS. As knowledge about the morphology of intrahepatic CPSS increases with the use of computed tomography (CT) it may be that we can identify some animals that would benefit specifically from surgical treatment and some specifically from endovascular coil embolization, although this is unproven.

There are still many unanswered questions regarding the management of dogs with intrahepatic CPSS. Large randomised prospective studies are needed to compare treatments to determine which are associated with the best outcome for dogs. Further investigation is also needed to develop consistent and validated outcome measures.
Conflict of interest

None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.
References


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Oxford Centre for Evidence-Based Medicine.


