



Does Adding Transdermal Nitroglycerine to Other Therapies Used for Management of Left-sided Congestive Heart Failure in Dogs Speed the Resolution of Clinical Signs?

A Knowledge Summary by

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Clinical bottom line

There is very weak veterinary clinical and experimental evidence based upon a limited number of studies to indicate that adding transdermal nitroglycerine to other therapies used for management of left-sided congestive heart failure in dogs speeds the resolution of clinical signs.

Question

Does adding transdermal nitroglycerine to other therapies used for management of left-sided congestive heart failure in dogs speed the resolution of clinical signs?

Clinical Scenario

Transdermal nitroglycerin is frequently recommended as an adjunct therapy in many canine treatment protocols for left-sided congestive heart failure due to its preload and afterload reducing effects. Does adding transdermal nitroglycerin to other therapies used for management of left-sided congestive heart failure in dogs speed the resolution of clinical signs?

The Evidence

There is no evidence in the literature to suggest transdermal nitroglycerin speeds resolution of clinical signs in dogs with pulmonary oedema secondary to left-sided congestive heart failure. There is equivocal to weak evidence that transdermal nitroglycerin reduces systolic and/or mean arterial blood pressure in dogs. There is no evidence that transdermal nitroglycerin has any effect on resolution of any clinical signs of left-sided congestive heart failure. Although there are no reports of adverse harm associated with transdermal nitroglycerin, there are insufficient clinical studies to be able to state nitroglycerin does not have any adverse affects in dogs.

Summary of the evidence

Nakayama (2007)	
Population:	mixed breed dogs with Seller's grades 2+ or 3+ mitral regurgitation
Sample size:	9 dogs
Intervention details:	Mitral regurgitation was produced by surgical disruption of the mitral valves. Five months after production of mitral regurgitation, left atrial dimension and ventricular function were measured using echocardiography/Doppler and left ventricular micromanometry. Nine mixed breed dogs weighing 21-32 kg were administered butorphanol (0.05 mg/kg IM) prior to the start of each study. Enalaprilat, nitroglycerin, ouabain, milrinone or placebo (IV saline, There was a one-week washout period between arms of the study to ensure at least 10 half-lives between exposures. Recordings were obtained, along with an ECG, during baseline and 30 minutes after

	dogs received IV (in random sequence) 0.3 mg/kg enalaprilat, 20mg/kg ouabain, or 100mg/kg of milrinone; or 2 inches of 2% nitroglycerin paste applied to the skin of the inner thigh over an area of 16 cm ² . All dogs also were given an IV (saline) and a transdermal placebo (Vaseline). Dogs were studied 1 hour and 2 hours after application.
Study design:	Randomised controlled clinical trial
Outcome studied:	The effect of 4 different cardioactive drugs on left ventricular function in dogs with mitral regurgitation of 5 months duration. Parameters studied included intracardiac dimension, peak aortic flow, left atrial diastolic and systolic function.
Main findings: (relevant to PICO question):	<ul style="list-style-type: none"> When compared to placebo (Vaseline), transdermal nitroglycerin failed to produce an effect on any of the parameters studied.
Limitations:	Small sample size. Surgically induced mitral regurgitation may not accurately reflect clinical mitral endocardiosis. No animals had clinical signs of congestive heart failure.

Kanda (1995)	
Population:	Healthy Beagle dogs
Sample size:	5 dogs in each group
Intervention details:	There were 3 groups; Nitroglycerin tape at 2.5 mg/kg (NT-I, 5 mg nitroglycerin per 5 x 10 cm ²) with placebo capsule, nifedipine given orally (3mg/kg) with placebo tape, and a control group that received a placebo (blank) capsule orally and placebo tape. Placebo and nitroglycerine tape were applied to a clipped area of skin on the chest of healthy beagle dogs.
Study design:	Prospective study (non-randomised, non-blinded)
Outcome studied:	The effect of nitroglycerin tape compared to placebo tape on blood pressure (systolic and diastolic), heart rate and coronary blood flow in healthy beagle dogs. Baseline values recorded for 1 hour before drug administration and then at 30 min, 1 hour and every hour until 9 hours. Parameters were measured again 1 hours following removal of tape.
Main findings: (relevant to PICO question):	<ul style="list-style-type: none"> Systolic blood pressure was decreased by 10-15%, compared to baseline, with application of nitroglycerin tape in awake healthy instrumented beagle dogs. The decrease was noted 1 hour after application, persisted for the duration of the study and returned to baseline values within 1 hour of removing the tape. Calculated (not directly measured) mean arterial pressure decreased 4-5 %. Diastolic blood pressure and heart rate were not affected.

	<ul style="list-style-type: none"> • Changes were noted 30 minutes after the application of nitroglycerin tape and remained constant for 8h. • No changes from baseline parameters were noted in the control group.
Limitations:	Small sample size may have failed to detect true differences that existed between groups or within groups. Decrease in blood pressure provides indirect evidence of the efficacy of nitroglycerin which does not equate to clinical improvement. Dogs were healthy and did not have any clinical signs of congestive heart failure.

McKie (2014)	
Population:	Male mongrel dogs with induced mild left ventricular dysfunction.
Sample size:	Three study groups with 7 dogs in each group (intravenous M-ANP, nitroglycerin, and vehicle 0.9% normal saline)
Intervention details:	Mild left ventricular dysfunction was induced via right ventricular pacing at 180 beats per minute for 10 days in male mixed mongrel dogs. RV pacing was terminated the day of the study and dogs were anesthetized with pentobarbital sodium (15mg/kg IV), intubated and ventilated. Hypertension was induced in instrumented dogs via IV administration of Angiotensin II (40 mg/kg/1min). Dogs were then administered either M-ANP (30 pmol/kg/min), nitroglycerin (10 ug/kg IV) or 0.9% normal saline at a rate of 1ml/min.
Study design:	Prospective experimental study under anaesthesia (non-randomised, non-blinded)
Outcome studied:	Blood pressure, PCWP, systemic vascular resistance, left ventricular filling pressures, heart rate, cardiac output.
Main findings: (relevant to PICO question):	<ul style="list-style-type: none"> • Nitroglycerin significantly decreased mean arterial blood pressure, PCWP, systemic vascular resistance and left ventricular filling pressures. • No effect on heart rate or cardiac output.
Limitations:	Nitroglycerin was administered IV, not topically. Sample size was small. Study was not blinded or randomised. Experimentally induced heart failure was studied, not naturally occurring heart failure. Evidence provided that IV nitroglycerin reduced preload and afterload but this does not equate to improvement in clinical signs.

Parameswaran (1999)	
Population:	Healthy anaesthetised dogs
Sample size:	15 dogs
Intervention details:	Sonomicrometer crystals were applied to the spleen in each dog and a pressure-measuring catheter was inserted into a splenic vein. A

	2.5cm strip of transdermal 2% nitroglycerin ointment was applied to the inner surface of the pinna in 10 dogs and 5 additional dogs (control group) were given only petrolatum.
Study design:	Non-randomised clinical trial
Outcome studied:	Splenic dilatation in healthy dogs anaesthetised with alpha chloralose after transdermal application of nitroglycerin. Splenic dimension and venous pressure were measured for 10 minutes before application and time from application of transdermal nitroglycerin to the initial change in dimension and to the maximal change in dimension (measured to the nearest second).
Main findings: (relevant to PICO question):	<ul style="list-style-type: none"> • Splenic dimension increased significantly from baseline in all 10 dogs receiving transdermal nitroglycerin. • Splenic enlargement was noted within 482 ± 652 seconds after application of transdermal nitroglycerin with maximal dilatation at 861 ± 632 seconds. • Splenic venous pressure did not change significantly in dogs receiving transdermal nitroglycerin or in control dogs.
Limitations:	Animals were healthy and anaesthetised with alpha chloralose, whose physiologic effects are not well characterized in the literature for any species. Results of the present study may not translate to un-anaesthetised dogs with left-sided congestive heart failure.

Appraisal, application and reflection

Given studies are lacking with regards to the efficacy of transdermal nitroglycerin when included as an adjunct treatment to other therapies in dogs with left-sided congestive heart failure, its use cannot be recommended in the management of these cases at this time. Future clinical studies are needed to evaluate the safety, efficacy and ideal dosage of transdermal nitroglycerin in the treatment of dogs with left-sided congestive heart failure.

Methodology Section

Search Strategy	
Databases searched and dates covered:	Pubmed Platform 1973- Week 1 2017], CAB Abstracts <1973 to 2016 Week 51>
Search terms:	<p>Pubmed</p> <ol style="list-style-type: none"> 1 Search (((glyceryl trinitrat*) OR glyceryltrinitrat*) OR trinitrat glycerin*) OR nitro glycerin*) OR nitroglycerin* 16518 2 Search (((((((heart) OR cardiac) OR CHF) OR cardio*) OR left ventricular) OR left ventricle*) OR LV) OR heart diseases) OR cardiovascular diseases 2866548 3 Search (((((dog) OR dogs) OR canine) OR bitch*) OR canis) OR bitches 351249 4 Search ((transdermal) OR cutaneous) OR ointment

	185703
	<p>CAB Abstracts:</p> <ol style="list-style-type: none"> 1. ("glyceryl trinitrat*" or glyceryltrinitrat* or "trinitro glycerin*" or trinitroglycerin* or "nitro glycerin*" or nitroglycerin*).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes] (374) 2. (heart or cardiac or CHF or cardio* or "left ventricular" or "left ventricle*" or "left ventrical*" or "LV").mp. or heart diseases/ or cardiovascular diseases/ [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes] (151135) 3. (dog or dogs or canine or bitch*).mp. or dogs/ or canis/ or bitches/ (192085) 4. 1 and 2 and 3 (16)
Dates searches performed:	22/12/2016 (CAB) 02/01/2017 (Pubmed)

Exclusion / Inclusion Criteria	
Exclusion:	Study design did not involve dogs and/or was not relevant to the research questions asked
Inclusion:	Any relevant primary veterinary research or systematic review which compared transdermal nitroglycerine to other therapies to answer the following question; "Does adding transdermal nitroglycerine to other therapies used for management of left-sided congestive heart failure in dogs speed the resolution of clinical signs?"

Search Outcome							
Database	Number of results	Excluded – Did not address the PICO	Excluded – Proceedings and review articles with no evidence	Excluded – Given IV, did not compare groups, and did not address clinical question	Excluded – Single case report with no evidence to the question	Duplicate results	Total relevant papers
PubMed	10	6	0	0	0	0	4
CAB Abstracts	16	0	6	6	2	2	0
Total relevant papers when duplicates removed							4

CONFLICT OF INTEREST

The author declares no conflict of interest.

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