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Laparoscopic adipose-derived stem cell harvest technique with bipolar sealing device: Outcome in 12 dogs

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Abstract

Objective: This study aimed to describe the technique and clinical outcomes in dogs undergoing Laparoscopic Adipose-Derived Stem Cell Harvest via bipolar sealing device (LADSCHB) for degenerative orthopaedic and neurologic disease.

Study Design: Descriptive retrospective case series.

Animals: Eleven dogs with orthopaedic disease and one dog with degenerative spinal disease were enrolled in the study.

Methods: Medical records of dogs undergoing LADSCHB were reviewed for signalment, weight, reason for the procedure, anaesthesia time, surgery time, other procedures performed, post-operative pain protocols, incision size, amount of adipose tissue collected, number of viable cells collected, days to discharge, short-term complications, and owner satisfaction.

Results: The median weight of the population was 34.2 kg (range 9.2–62 kg), the median surgery time was 39 min (range 15–45 min), mean incision length was 2.5 cm, the median amount of adipose collected was 60 g, and the median number of viable stem cells was 21 million cells. Conversion to open laparotomy was not needed. The most common reason for the harvest was osteoarthritis of the elbow (8/12 cases). Nine cases had other procedures performed at the same time as the harvest. No complications were noted during the procedure or within the post-operative period. All owners surveyed were satisfied with the laparoscopic harvest procedure.

Conclusions: LADSCHB was technically feasible, productive, and not associated with any complications. This procedure was performed rapidly and was paired with other surgical procedures.

Clinical Significance: LADSCHB allows for stem cell harvest with commonly utilized laparoscopic equipment. This surgical technique could lead to the increased ability to treat patients with diseases that benefit from stem cell therapy.

KEYWORDS
adipose-derived mesenchymal stem cells, laparoscopic-assisted surgery, laparoscopy, multipotent mesenchymal stromal cells

1 | INTRODUCTION

Stem cell therapy has become a burgeoning field in human and veterinary medicine with over 270,000 published articles according to a PubMed online search as of November 2020. Stem cells were first identified in embryonic tissue and bone marrow but have since been identified and isolated from most adult tissues including adipose tissue (Luyten, 2004; Parker & Katz, 2006). Pluripotent and multipotent cells have been investigated for a wide variety of disorders in humans including: neurologic disorders (Sarveazad et al., 2014), brain ischemia (Chung et al., 2015), cardiac infarction (Otsuki et al., 2015), stroke (Chi et al., 2016), wound healing (Condé-Green et al., 2016), osteoarthritis (Chang et al., 2016), Crohn's disease (De la Portilla et al., 2013), and many others. Adipose-derived stem cells (ADSC), a type of mesenchymal stem cell, have been used in veterinary medicine since 2003 for treatment of tendon injuries and osteoarthritis (Black et al., 2007, 2008; Guercio et al., 2012; Harman et al., 2016; Mobasheri et al., 2009; Smith et al., 2003; Vilar et al., 2014). Treatments for ocular, gastrointestinal and neurologic disease with this technique are also being investigated (Y. Kim, Lee, et al., 2016; H.-W. Kim, Song, et al., 2016). The Food and Drug Administration (FDA) has recently increased regulations regarding these treatments in human and veterinary medicine in order to ensure safety, efficacy and quality control (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-218-cell-based-products-animal-use). Currently, there are no FDA-approved veterinary cell-based therapies, but there are ongoing FDA-registered clinical trials.

Mesenchymal stem cells are considered multipotent because of the capacity to self-renew by dividing and to develop into multiple specialized cell types present in a specific tissue or organ. The benefits of ADSC over other types of mesenchymal sources (bone marrow, muscle, etc.) include the ease of removal and amount of tissue that can be harvested. Most ADSC therapies include stromal vascular fractions as well as the cells themselves. Stromal vascular fraction (SVF) derived from adipose tissue contains a heterogeneous mixture of cells and other biologically active components including endothelial progenitor cells, pericytes, immune cells, fibroblasts, growth factors, and cytokines (Black et al., 2007; Lin et al., 2010). The growth factors within SVF support angiogenesis, tissue remodelling, and differentiation and can have immune-modulatory and anti-apoptotic effects (Lin et al., 2010). The reported mechanisms of action of ADSC themselves include trophic support, immunomodulation, differentiation, homing, revascularization, and anti-apoptosis among others (Varma et al., 2007).

In clinical veterinary medicine, the use of stem cells has been popularized mostly by anecdotal evidence but a growing number of clinical, research-based and review publications have been published recently (Black et al., 2007, 2008; Fortier & Travis, 2011; Guercio et al., 2012; Harman et al., 2016; Y. Kim, Lee, et al., 2016, Kiefer et al., 2015; H. Kim et al., 2012; Pérez-Merino et al., 2015; Vilar et al., 2014; Whitworth & Banks, 2014). Reports of use in research-based and naturally occurring diseases include clinical studies on osteoarthritis in dogs (Canapp et al., 2016; Cuervo et al., 2014; Guercio et al., 2012; Harman et al., 2016; Vilar et al., 2014; Yun et al., 2016), one study on keratoconjunctivitis sicca in dogs (Villatoro et al., 2015), inflammatory bowel disease (Pérez-Merino et al., 2015), neurologic disease (Y. Kim, Lee, et al., 2016), and studies regarding chronic kidney disease in cats among others (Quimby et al., 2011, 2013, 2016). Three of these studies do include the use of platelet-derived therapies as well as ADSC illustrating the difficulty in acquiring clear data on this modality. While the numbers are small in many of these studies and most lack control populations, they highlight the great interest for use of ADSC as a treatment modality.

Originally harvest locations for adipose tissue in veterinary medicine were described as caudal to the scapula, inguinal fat pad, or falciform (Black et al., 2007). The first two options were originally deemed less invasive as they did not require an incision into a cavity, but in the author's experience tissue yields were low and post-operative complications such as seromas and incisional inflammation were common. Differences between harvest locations and stem cell number and viability have also been found in some studies (Astor et al., 2013; Bahamondes et al., 2017; Requicha et al., 2012). Subcutaneous tissue produced higher numbers of viable stem cells compared to falciform tissue in one report but lower numbers when compared to omental tissue in a separate study (Astor et al., 2013; Bahamondes et al., 2017). Differences in cell proliferation potential and senescence have also described an increase in cell productivity in visceral compared to subcutaneous locations.

Due to these factors, falciform and omental tissue have become the preferred location, but traditional collection methods require an abdominal incision similar to an exploratory incision to remove the entire falciform. As laparoscopic procedures have become more available in veterinary medicine, the application of this minimally invasive technique for ADSC harvest is logical. Minimally invasive techniques have the benefits of decreased morbidity (decreased pain, decreased infection rate, improved cosmesis), decreased hospitalization, and improved visualization compared to other techniques (Devitt et al., 2005; Mayhew et al., 2012). A study by Hoddinott et al. described laparoscopic-assisted falciform extirpation with a bipolar sealing device for a case of falciform hemangiosarcoma (Hoddinott et al., 2015). Recently, a study using laparoscopic morcellation on five client owned dogs reported viable stem cell harvest with no appreciable morbidity (DePompeo et al., 2020). The use of a laparoscopic morcellator device is not common in small animal surgical practices, and this may dissuade clinicians from attempting this procedure. The objective of this study was to describe the technique and short-term surgical outcomes of dogs undergoing laparoscopic ADSC harvest with a bipolar vessel sealing device (LADSCHB) for the treatment of degenerative orthopaedic and neurologic disease.

2 | MATERIALS AND METHODS

Records from a large specialty hospital were reviewed for any patient undergoing LADSCHB from 2012 to 2015, and 12 records were identified. Data retrieved from the records included signalment, weight, reason for the procedure, anaesthesia time, surgical time,

other procedures performed concurrently, post-operative pain control protocols, incision size, amount of adipose tissue collected (grams), number of viable doses, days to discharge, complications (incisional seroma, pain, discharge of any type, dehiscence of any layer), and owner satisfaction with procedure evaluated by follow-up phone calls. Each "dose" is targeted to contain 3 million stem cells per company (VetStem Biopharma, Poway, CA, USA) protocol. Anaesthesia time was defined as the time from aesthetic induction to extubation. Surgical time was defined as the time from first incision to last suture placement at closure. Aesthetic induction medications were determined by the lead veterinarian on the case and monitoring followed standard of care methods (blood pressure, heart rate, end tidal CO_2, etc.).

3 | SURGICAL TECHNIQUE

The surgical technique for the LADSCHB cases was as follows: the patient was placed in dorsal recumbency with the ventral midline abdomen shaved and aseptically prepped. Depending on other procedures being performed, the hair was only clipped from the nipple line to the opposite nipple line from the xiphoid to the pubis. A single incision port (SILS Port, Medtronic Covidien Minneapolis, MN, USA) was placed at midline halfway between the umbilicus and pubis or immediately cranial to the prepuce via Hasson technique (Dupree, 2015). Briefly, a 2–3 cm incision was made through the skin and subcutaneous tissues, stay sutures were placed on both sides of the linea, and the linea was incised to allow for introduction of the SILS port. To aid in placement of the SILS port and visualization of the abdomen, the falciform at the incision site was carefully dissected out with electrocautery and placed into a sterile sample tube. The SILS port was then placed into the abdominal cavity, insufflation was performed to 8–10 mm Hg CO_2, and a 5 mm 0-degree telescope was inserted into the abdomen for initial explore. A second paramedian 5 mm port was then placed under visualization on the left side of the patient (Figure 1). This paramedian port was used for visualization by the telescope during dissection of the falciform cranially (Figure 2). Once the telescope was inserted laterally, a 5 mm LigaSure (Medtronic) device was placed within the SILS port and used to carefully dissect the falciform fat in a caudal to cranial direction (Figure 3). A laparoscopic grasper was then inserted into the SILS port and the fat grasped (Figure 4). The SILS port was then gently removed over the instrument, and the grasper was then carefully exteriorized with the falciform fat. The tissue was then sectioned and placed into sterile collection tubes, which each hold 30 g of tissue/45 ml (VetStem Biopharma, Poway, CA, USA). The number of tubes collected for every patient varied based on the amount of available tissue. If patients had falciform removed during a prior surgical procedure, omentum was harvested to fill the tubes. Omentum was harvested by grasping the greater leaf with a laparoscopic babcock and exteriorizing it from the abdominal incision. The LigaSure was then used to remove omentum in sections. A complete omentectomy was never performed due to the importance of the omentum for abdominal surveillance. Submission of at least two full tubes (60 g tissue) is recommended by the company to produce enough cells that can be stored for later use

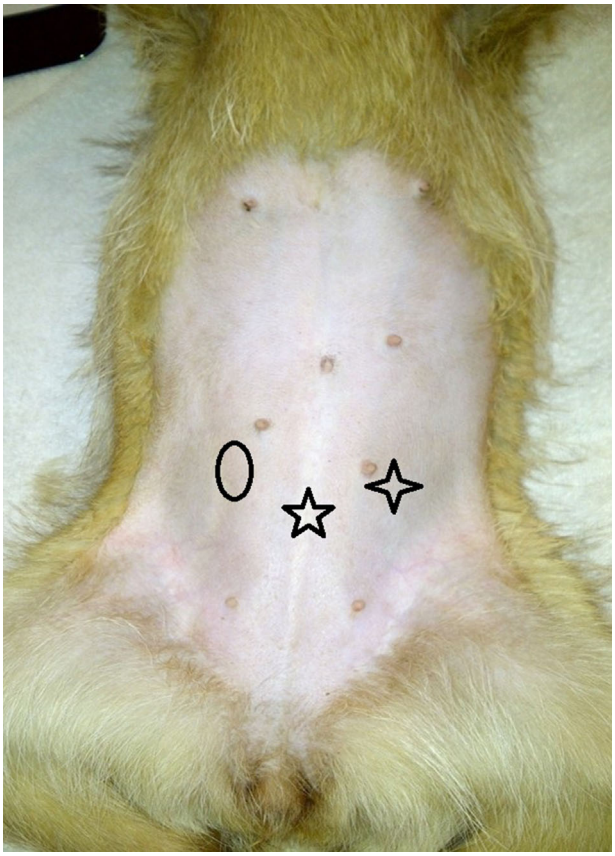

FIGURE 1 Photograph of port placement for Laparoscopic Adipose-Derived Stem Cell Harvest via bipolar sealing device (LADSCHB). Five-point star = single incision laparoscopic surgery (SILS) port for initial insufflation, telescope, and instruments. Four-point star = 5 mm port for placement of telescope. Oval = port placement if additional instrumentation needed

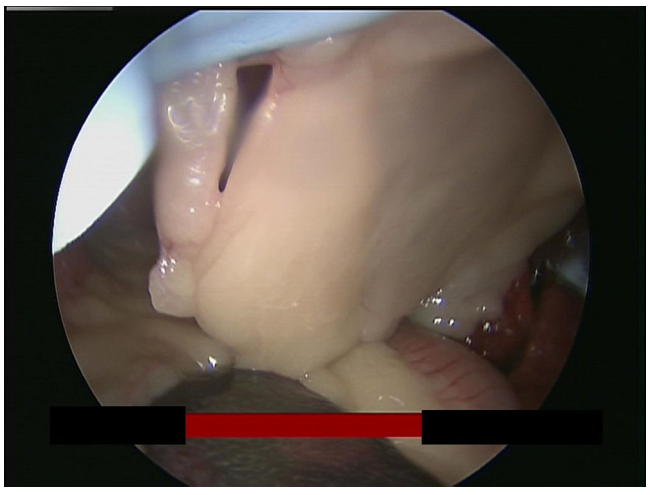

FIGURE 2 Intraoperative view of the falciform. Telescope has been placed in the left paramedian port, and the single incision laparoscopic surgery (SILS) port is at the caudal aspect of the falciform (left of the photograph)

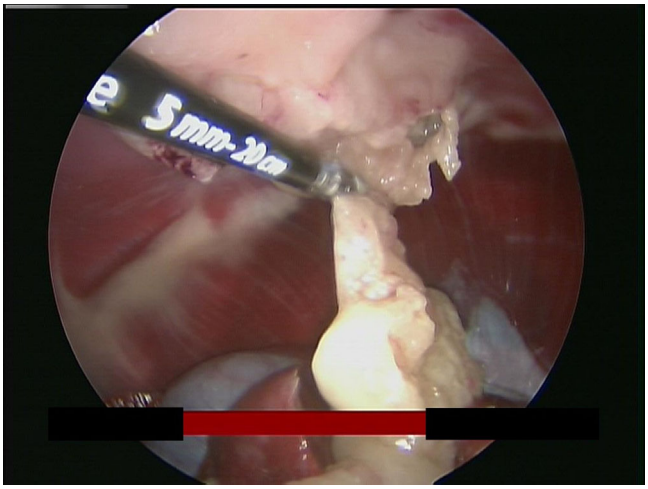

FIGURE 3 Intraoperative view of the falciform being dissected from the body wall with a 5 mm Dolphin-tipped Ligasure. Telescope in in the left paramedian port and LigaSure in the midline single incision laparoscopic surgery (SILS) port

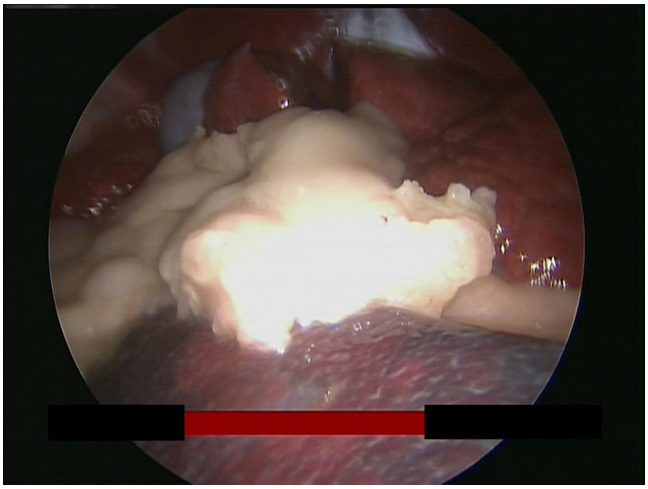

FIGURE 4 Intraoperative view of the resected falciform lying on the spleen. Telescope is through the midline single incision laparoscopic surgery (SILS) port

and used in the immediate future based on previous studies from this company (Black et al., 2007, 2008; Harman et al., 2016).

Intraoperative complications were reported and considered major if conversion to an open procedure occurred, or patient outcome was affected (death). Records were reviewed for post-operative pain control, and the methods varied based on surgeon preference and the procedures being performed. Postoperative complications were considered minor or major. Minor complications included incisional swelling/redness. Major complications included incisional infection as defined by purulent discharge and pain at the incision site, herniation of abdominal structures through the incision or incisional dehiscence. Owner satisfaction with the laparoscopic procedure was assessed at suture removal follow-up appointment by a scale of 1–3 with 1 = not satisfied, 2 = neutral, and 3 = satisfied. This information was present within the owner discussion portion of the medical record. Due to the small sample size, descriptive statistics were performed with means and medians with ranges reported.

4 | RESULTS

Of the 12 patients admitted for LADSCHB, the mean age was 5.6 years (median = 4.5, range of 7 months old to 13 years old), and the mean and median weight was 34.2 kg (range of 9.2–62 kg). Multiple breeds were represented (see Table 1). The reason for the MSC harvest included management of bilateral elbow dysplasia in eight dogs, chronic stifle arthritis (one), generalized osteoarthritis (two), and degenerative myelopathy (one). The mean anaesthesia time was 190 min (median = 197.5 min, range 81–285 min), and the mean laparoscopic surgical time was 38.4 min (median = 39, range of 15–45 min). Nine of the patients (75%) had a secondary procedure during the stem cell harvest, five of which had three or more procedures during the same anaesthetic period (see Table 1). The mean and median incision length for the LADSCHB procedures was 2.5 cm (range 1.5–4 cm), the mean and median amount of tissue collected was 66 and 60 g, respectively (range 15–120 g), as estimated by the number of visually full tubes collected, and the mean and median number of collected doses was 8.4 and 7, respectively (range of 1–18), with approximately 3 million cells per dose per company guidelines. Five of 12 patients required the addition of 15–20 g of omentum to complete the desired amount of tissue (60 g) due to previous abdominal surgeries.

In-hospital and send home post-operative pain management varied based on procedures performed and patients preoperative pain status (see Table 1). The neurologic patient was on steroids at the time of the procedure and continued in the post-operative period due to their neurologist's recommendations. Four patients, all undergoing 2–3 additional procedures, were discharged with a 50 μg fentanyl patch (Duragesic, Janssen Pharmaceuticals, Belgium) for 3 days as well as tramadol and a non-steroidal anti-inflammatory. The mean discharge time was 1.3 days (median = 1, range 0–3). There were no intraoperative conversions to open laparotomy or other major complications noted. Two of the 12 patients (17%) of patients presented to suture removal with minor incisional inflammation. No major post-operative complications were noted, and all owners were satisfied (score of 3) with the LADSCHB procedure when surveyed at the 2-week recheck exam.

5 | DISCUSSION

The reported technique for laparoscopic ADSC harvest is technically feasible, productive, and was not associated with any complications. Owners of all 12 dogs were happy with the procedure and would recommend it to friends or family members. The described technique allows for excellent visualization of the falciform attachment to the body wall, which maximizes the retrieval of as much of the falciform as possible. This procedure can be combined with other procedures or

TABLE 1 Patient data and treatments

Signalment	Weight (kg)	Additional surgery performed	Anaesthesia time	Surgery time	Postoperative pain medication (in-hospital)	Discharge medication	Hospitalization (days)
1.5 yo MI Lab	31.4	bilateral elbow arthroscopy laparoscopic gastropexy	285	15	hydromorphone, Metacam (0.1 mg/kg PO SID)	Fentanyl patch (50 μg), Tramadol (4 mg/kg PO TID), Metacam	1
8 yo SF Gldn	37.8	Bilateral elbow arthroscopy	142	25	Fentanyl CRI at 2–3 micrograms/kg/h for up to 12 h, hydromorphone, Carprofen (2.2 mg/kg PO BID)	Tramadol, Carprofen, Gabapentin (10 mg/kg PO TID)	1
4 yo SF Rott	42.9	None	81	40	hydromorphone	Tramadol	0—discharged same day
10 yo MC Boxer	35.2	none	86	45	hydromorphone, tramadol	Tramadol	2
0.8 yo SF GSD	33.2	bilateral elbow arthroscopy, laparoscopic gastropexy	268	35	Fentanyl CRI, Metacam	Fentanyl patch (50 μg), Tramadol, Metacam	2
0.8 yo MI GSD	30.5	bilateral elbow arthroscopy, UAP removal, laparoscopic gastropexy	285	30	Fentanyl CRI, Metacam	Fentanyl patch (50 μg), Tramadol, Metacam	2
10 yo MC Mastiff	62	Bilateral parathyroidectomy Mass removal	265	40	Fentanyl, Tramadol	Fentanyl patch (50 μg), Tramadol	3
10 yo MC Wheaten	20.2	laparoscopic liver biopsy, bilateral elbow arthroscopy	130	38	Prednisone (0.5 mg/kg PO SID), Fentanyl CRI, Methocarbamol (20 mg/kg PO BID), Gabapentin	Tramadol, Prednisone, Gabapentin	1
13 yo MC ChowX	27.4	None	88	45	Hydromorphone, Tramadol	Tramadol	0—discharged same day
5 yo MI Gldn	43	Bilateral elbow arthroscopy	253	73	Fentanyl CRI, Carprofen	Gabapentin, Carprofen	1
2 yo FS GSD	37.8	Bilateral elbow arthroscopy	273	45	Fentanyl CRI, Tramadol, Metacam	Tramadol, Metacam	2
3 yo MC TerrierX	9.2	Unilateral medial patellar luxation	135	30	Fentanyl CRI, Metacam	Tramadol, Metacam	1

be performed on an outpatient basis, facilitating the use of stem cells in patients that may benefit from regenerative medicine therapies.

Mesenchymal stem cell therapy is an area of significant research in both veterinary and human medical fields currently and may hold potential for the treatment of a wide array of diseases (Canapp et al., 2016; Chang et al., 2016; Chi et al., 2016; Chung et al., 2015; Condé-Green et al., 2016; Cuervo et al., 2014; De la Portilla et al., 2013; Guercio et al., 2012; Harman et al., 2016; H.-W. Kim, Song, et al., 2016; Y. Kim et al., 2012; Otsuki et al., 2015; Pérez-Merino et al., 2015; Quimby et al., 2011, 2013, 2016; Sarveazad et al., 2014; Vilar et al., 2014; Villatoro et al., 2015; Yun et al., 2016). With adipose tissue being readily available in both human and veterinary populations, its use can be recommended to obtain the necessary cells. Stem cells are most often found in blood vessels (Aust et al., 2004; Jurgens et al., 2008; Lin et al., 2010; Varma et al., 2007), and adipose tissue is known for its high density of capillaries making it a rich potential source. As described in multiple studies, there are differences between the number of viable stem cells per gram of adipose tissue and the cell proliferation potential and senesance (Astor et al., 2013; Requicha et al., 2012). The recent study by DePompeo et al. demonstrated that falciform fat removed via morcellator had approximately the same number and viability of cells when compared to traditionally harvested falciform (DePompeo et al., 2020).

As there is no specific guideline recommended for the collection of adipose tissue for cell-based therapeutics, veterinarians and owners are left with many options. Five options for adipose tissue collection are currently available: traditional open approach, harvest from subcutaneous regions via lipoaspiration, a key-hole abdominal approach, and LADSCHB with either the morcellator or bipolar sealing technique.

Concerns over pain, activity restriction, and infection are all raised by owners with the traditional open method of adipose collection. Accessing the full falciform tissue by a traditional open approach requires recovery from a large ventral abdominal incision which may deter owners of patients most in need of regenerative medicine modalities. Older patients commonly have comorbidities that preclude certain medication options for chronic diseases (i.e., NSAIDs); therefor, owners may be reluctant to put them through a perceived difficult recovery. Young patients with slowly degenerative diseases, dysplasia's for example, may also benefit from these treatments, but owners can be averse to an invasive open procedure as their perception is that their pet may not use these cells for many years (Black et al., 2007, 2008, Harman et al., 2016; Cuervo et al., 2014). Minimally invasive procedures have the benefit of decreased pain scores and infection rates and high owner satisfaction in veterinary and human medicine (Devitt et al., 2005; Mayhew et al., 2012).

In people, lipoaspiration or liposuction is the most common procedure performed for ADSCH with many different techniques reported (Aust et al., 2004; Domenis et al., 2015; Jurgens et al., 2008). In veterinary medicine, there is one published report of lipoaspiration of subcutaneous adipose tissue that successfully cultured viable stem cells (Vieira et al., 2010), but this study did not discuss the clinical effects of the procedure on the patients (post-operative discomfort, swelling, incisional complications) or provide data regarding the number of viable cells per gram of material produced. Another limitation to the lipoaspiration technique arises in older dogs who may lack of adequate subcutaneous fat due to comorbidities.

In the key-hole abdominal approach, an incision of varying size (2–4 cm) is made on the ventral abdomen, and omentum is grasped and ligated or cauterized and used instead of falciform fat. The important functions omentum performs in the body, such as participation in the body's response to peritoneal injury or contamination (abdominal surveillance), are well-known, and if possible, it should be spared (Kirkby, 2003). A large amount of the omentum may need to be removed for adequate ADSC collection with this technique, potentially compromising the abdominal immune response. Another disadvantage of this technique is the inability to explore the abdominal cavity, limiting the opportunity to identify pathology. There are many benefits to laparoscopic collection over a key-hole open approach including full utilization of the falciform fat as a first line, decreased removal of omentum, and visualization of any post-collection bleeding. Laparoscopy also allows for excellent visualization of the peritoneum and surfaces of internal organs, which may reveal disease not previously appreciated. One important difference between the technique presented and the other laparoscopic techniques reported (morcellation) (DePompeo et al., 2020) is the amount of adipose tissue collected. On average, we collected 66 g of tissue (range 15–120 g) compared to 5 g in that study. While the authors do mention that further passes of the morcellator could be performed in theory to acquire more tissue, they did not do this to keep anaesthesia time to a minimum. As more work is done to determine if first passage cells are more potent than cultured cells (Shen et al., 2018) it may be beneficial to remove as much tissue as possible initially to gain the largest amount of tissue for future use. The morcellator device is also an added cost to a facility, and its use in small animal laparoscopy has only been reported in one experimental model of canine nephrectomy (Y. K. Kim et al., 2013). The bipolar sealing device that was employed in this study has become an invaluable tool in laparoscopic surgery in human and veterinary medicine. This device is currently used in laparoscopic procedures ranging from sterilization to cholecystectomy. The procedure described allows for greater use of this equipment and more clinical options for veterinarians treating chronic degenerative diseases.

According to our results, the described laparoscopic technique is well-tolerated by patients, with no complications noted or conversion to open procedures required. All owners were satisfied with the procedure and were pleased that it could be paired with other surgical procedures (gastropexy, arthroscopy, etc.) with minimal perceived discomfort. LADSCHB does have some technical challenges to keep in mind and in the authors experience it is important to place the SILS port as caudal as possible to allow for capture of the majority of the falciform fat. During collection, it may be necessary to lift the SILS port and body wall ventrally (towards the ceiling) and lever the hand controlling the LigaSure device dorsally (towards the floor) to encourage the LigaSure device to slide directly against the body wall as it travels cranially. Placing a third port (a second paramedian port) to aid in retracting, dissecting, or viewing is another possibility although it was not done in this cohort of patients (Figure 1).

The study's main limitations include a small sample size, short follow-up time, and the inability to compare in a prospective nature to open procedures. Due to the decrease in pain documented in many other studies, the traditional open approach was not actively promoted. Another limitation discussed in the previous study is the lack of follow-up laparoscopy to document adhesion formation in these patients (DePompeo et al., 2020). While clinically there was no evidence of this in the short term (no abdominal pain, abdominal disease such as intestinal obstructions), it would be interesting to document the differences in adhesion formation between all the abdominal techniques.

In conclusion, LADSCHB with a bipolar sealing device is safe, productive, can be performed rapidly, and paired with other surgical procedures. The procedure provides a feasible mechanism for ADSC collection for indications such as degenerative orthopaedic and neurologic disease in veterinary patients.

ACKNOWLEDGEMENT

None.

CONFLICT OF INTEREST

The author declares no conflict of interest.

AUTHOR CONTRIBUTIONS

As the sole author, I was the lead in the following roles: conceptualization, investigation, data curation, formal analysis, and writing and editing.

ETHICS STATEMENT

The author confirms that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this is a retrospective article with data mined from previous patients.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/vms3.816.

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