PAPER

Current fluid and blood product availability in small animal practices in the UK URN SR2019-0008

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Objectives: To investigate and discuss current fluid and blood products stocked in small animal practices in the UK.

Methods: An online survey was circulated to small animal veterinary practices across the UK. The survey included questions regarding the level of hospital care provided, the type of fluid and blood component products stocked, the most frequently restocked products, and the available options in the event that blood products were required but not stocked.

Results: There were 423 responses including 27 duplicates. The remaining 396 respondents represented a spectrum of practices including 19 referral practices. Crystalloids were stocked in all practices. Lactated Ringer's solution was the most frequently re-stocked product in 355 of 396 (90%) of practices. Where synthetic colloids were stocked, gelatin-based colloids (155/178 [87%]) were stocked in preference to hydroxyethyl starches (23/178 [13%]). Blood products were stocked by 81 of 396 (20%) of practices. If a blood product was required but not stocked, 31% of practices would use a pet blood banking service, 28% would use their own blood donors, and 21% would refer.

Clinical Significance: This study provides an insight into the fluid and blood products stocked and used by a selection of veterinary practices within the UK and serves as a baseline for ongoing research and decision-making in both veterinary practice and industry.

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INTRODUCTION

Fluid therapy has been an integral part of both human and veterinary medicine for decades, particularly in management of critically ill patients. Historically, 0.9% saline has been the most widely used crystalloid in people, however, in more recent years, many varieties of fluids have been developed with a range of different indications and there has been a shift towards use of balanced isotonic crystalloids. Balanced isotonic crystalloids have an electrolyte content closer to that of extra-cellular fluid and, when given intravenously, may have fewer adverse effects on acid-base balance than 0.9% saline (Drobatz & Cole 2008, Semler *et al.* 2018, Semler & Kellum 2019). With such an array of products available and such variation in practice type within veterinary medicine, fluid product provision can be complicated and most current literature does not comply with recommended evidence standards, making an evidence base difficult to establish (Muir *et al.* 2017).

Fluid therapy products available in veterinary medicine can be separated into two broad categories, crystalloid and colloid solutions. Crystalloids are aqueous solutions of small (<5 kDa) electrolytes and other soluble components, and are further classified as hypotonic, isotonic or hypertonic solutions, based on their tonicity relative to plasma. Their primary use is in replenishment of fluid deficits and catering for ongoing losses in the interstitial and intravascular spaces of dehydrated and hypovolaemic patients, respectively. Maintenance fluid products containing less sodium such as 0.45% NaCl with 2.5% dextrose are recommended for patients that are not eating or drinking, but do not have volume deficits or ongoing losses (Mazzaferro & Powell 2013).

Colloidal solutions, however, are relatively more expensive, can be allergenic and have known effects on coagulation and renal function in human and veterinary patients alike (Chan 2008, Mutter *et al.* 2013, Boyd *et al.* 2018). Nonetheless, there are indications in veterinary practice for the use of colloids. The high molecular weight of the dissolved colloid molecules contributes to oncotic pressure to retain water within the intravascular space (Pachtinger & Drobatz 2008). Colloids may be considered advantageous in the treatment of recurrent hypovolaemia and/or hypoproteinemia, particularly if the glycocalyx integrity is still preserved (Milford & Reade 2019). Colloids can be divided into natural products, such as plasma or albumin, and synthetic products including gelatins, hydroxyethyl starches (HES) and dextrans.

Progressions in the field of blood component therapy have enabled provision of safer, storable and more tailored products than whole blood (Davidow 2013). Increased availability of these blood products allows clinicians to make more individualised therapy plans for patients.

An increasing number of veterinary recommendations and guidelines are being generated to help practitioners make appropriate choices of fluid products (Shafford *et al.* 2013, Byers 2017). The same is true for blood products (Barfield & Adamantos 2011, Davidow 2013). While these often exemplify 'gold-standard' choices, they do not always reflect what is accessible or stocked in all practice settings. Much of the current veterinary literature regarding fluid therapy and blood products does not specifically focus on a UK population, and recommendations often involve products that are more readily available in North America. This study aims to investigate and discuss current fluid and blood products actually stocked and used in small animal practices in the UK.

MATERIALS AND METHODS

Ethical approval was obtained by the Social Sciences Research Ethical Review Board (SSRERB) at the author's institution. A survey was created on an online professional survey program (SurveyMonkey Professional Online Surveying Program [www.surveymonkey.com]) and was distributed to small animal practices across the UK via an email invitation sent between 28th February 2019-2nd March 2019. The email addresses were obtained from the RCVS website after using the search system to select for practices which treated both cats and dogs as a minimum. The survey was further circulated via social media. Participation was entirely voluntary, and the survey remained open until 26th March 2019. A £50 voucher prize draw was used as an incentive for completion of the survey.

The survey was designed to take less than 3 minutes to complete and could be answered by any member of the veterinary practice to help maximise response rates. Respondents were asked five questions as shown in Appendix 1; one pertaining to each of the following: the type of practice, all types of fluid products currently stocked, the fluid type that is most frequently restocked, the types of blood component therapy stocked (if any) and the procedure in the event that a blood component is required but not stocked. There was an option to provide a free text answer for further details or products stocked at the end of each question.

All free-text answers were reviewed and where necessary, combined with the primary dataset. Respondents categorised themselves as one of the following according to the amount of hospital care provided: branch/standalone practice (consults only), branch/standalone practice (+ routine procedures/imaging), hospital without onsite overnight care, hospital with onsite overnight care, 24-hour hospital, referral hospital, and 24-hour referral hospital. For subsequent analysis, these were grouped into first opinion (consults only, consults ± routine procedures, hospital ± overnight care and 24-hour hospitals) and referral (referral hospitals and 24-hour referral hospital) practice.

Statistical analysis

Data were compiled into commercially available software (Microsoft Office 2010. Microsoft Excel (version 14). Microsoft Corporation, 2010. Redmond, WA) and percentages were calculated from frequency data.

RESULTS

The online survey was emailed to 2994 small animal veterinary practices and 423 responses were received. The survey had a completion rate of 99.8% (422/423); a single respondent did not complete the final question. After incomplete or duplicate responses from individual practices were removed, the total number of valid responses was 396 of 423 (93.6%). Duplicates were identical in 26 of 27 (96.3%) responses. Of these responses, the majority were from first opinion practices performing routine procedures (256/396 [64.6%]). The remaining proportions are displayed in Fig 1.

Fluid therapy products

A summary of the most frequently stocked crystalloid products stocked by practices can be seen in Fig 2. Every practice stocked lactated Ringer's solution (LRS) (396/396 [100.0%]) and the majority of practices also stocked 0.9% NaCl (saline) (386/396 [97.5%]). Plasmalyte-148 was stocked by 6 of 396 (1.5%), Normosol R by 1 of 396 (0.3%), Plasmalyte-56 by 3 of 396 (0.8%) and Normosol M by 0 of 396 (0.0%) practices. Sterile water for injection was stocked in 346 of 396 practices (87.4%).

The most frequently stocked hypotonic crystalloid solution was 0.18% NaCl +4% dextrose which was present in 111 of /396 (28.0%) of practices. Mannitol was the most frequently stocked hyperosmolar agent (169/396 [42.7%]), followed by hypertonic saline (100/396 [25.3%]). Neither mannitol nor hypertonic saline were stocked in 194 of 396 (49.0%) practices.

Synthetic colloids (SCs) were reportedly stocked in 45% practices (178/396), of which Gelofusine (155/178 [87.1%]) was the most popular, followed by Voluven (23/178 [13%]). Eleven practices (11/178 [6.2%]) kept more than one type of SC in stock, and one of these products was always Gelofusine.

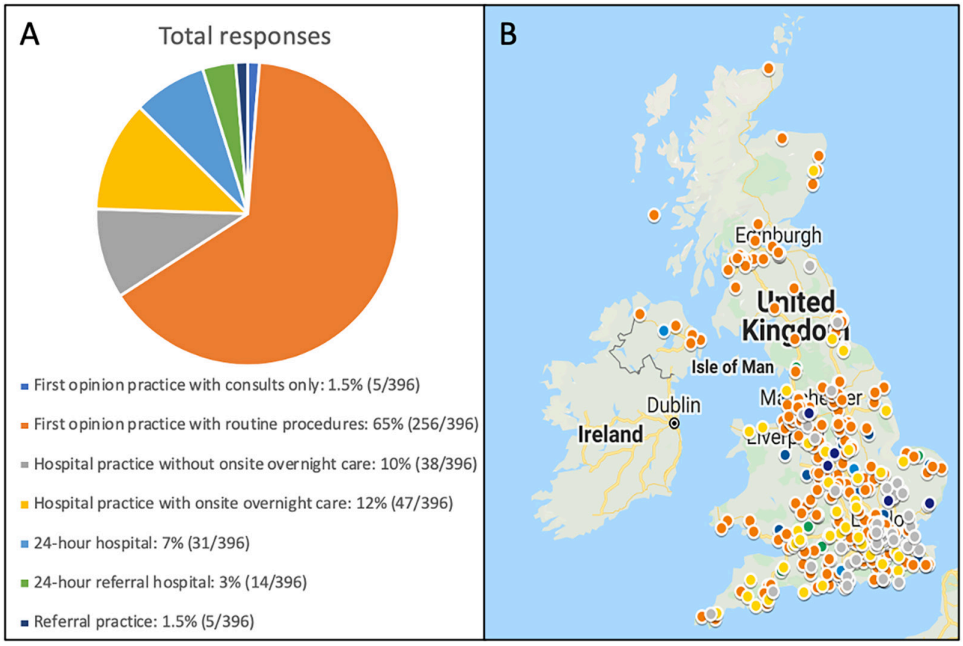

FIG 1. (A) The number of practice types that completed the survey. (B) Distribution of responding practices across the UK

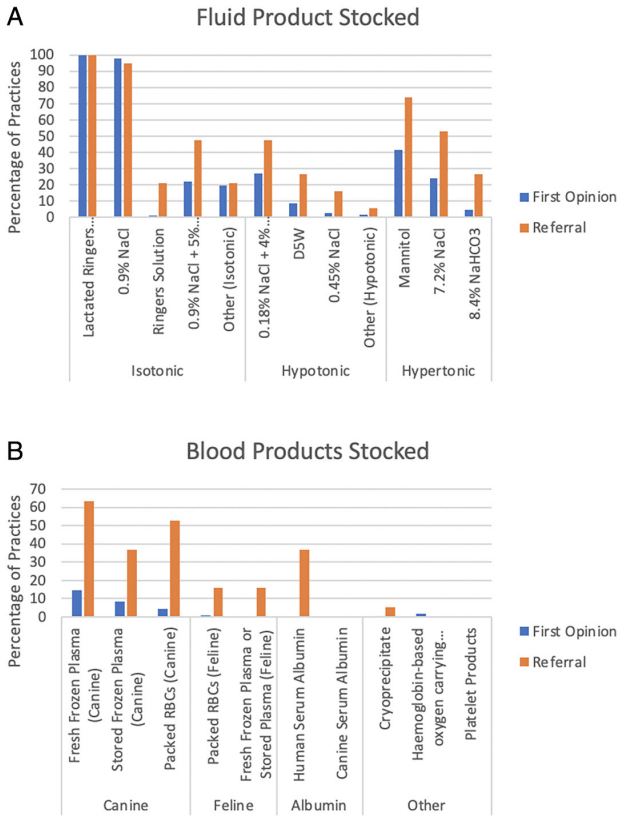

FIG 2. (A) Summary of crystalloid products stocked by practices. Practices have been grouped into first opinion and referral practice. NaCl, sodium chloride; NaHCO3, sodium bicarbonate. (B) Summary of blood products stocked by practices. Practices have been grouped into first opinion and referral practice. RBCs red blood cells

No clinic stocked more than two SCs. Dextrans and Volulyte were stocked in 2 of 396 (0.5%) and 2 of 396 (0.5%) practices, respectively.

When asked to select which fluid product was most commonly used/restocked in their veterinary practice, the majority of respondents selected LRS (355/396 [89.7%]). 0.9% sodium chloride (saline) was the second most commonly replaced fluid (38/396 [9.6%]) and the remaining three respondents answered with 0.18% NaCl with 4% dextrose.

Blood products

A summary of the blood products stocked by all practices can be seen in Fig 3. Blood products were stocked by 20.0% of practices (81/396). Canine fresh frozen plasma was the most frequently stocked blood product (67/396 [16.9%]), followed by canine stored frozen plasma (38/396 [9.6%]) and canine packed red blood cells (27/396 [6.8%]). Feline packed red blood cells and feline fresh frozen or stored plasma were stocked by 6 of 396 (1.5%) and 4 of 396 (1.0%) practices, respectively. Human serum albumin (HSA) was stocked by 8 of 396 (2.0%) and canine serum albumin (CSA) was stocked by one practice. Cryoprecipitate was stocked in 2 of 396 practices (0.5%) and no practices stocked platelet products. Haemoglobin-based oxygen carrying solutions were reported to be stocked in 6 of 396 practices (1.5%).

The final question asked what practices would usually do in the event that a patient required a blood product but no appropriate products were stocked. The total number of responses for this question was 363. Using a pet blood bank was the single most popular choice (113/363 [31.1%]), followed by using blood donors from their records (104/363 [28.6%]). Twenty-one percent of practices would refer their patients (77/363) and a further 60 of 363 practices (16.5%) transferred their patients to a main branch or nearby hospital. Sixteen practices gave free-text answers and commented that they would use combinations of the above on a case-by-case basis.

DISCUSSION

Crystalloids

In recent years, research has raised concerns over the safety of saline compared to more physiologically balanced crystalloid solutions, such as LRS (Semler & Kellum 2019). These studies include recent clinical trials in people which have demonstrated higher rates of adverse kidney events and death in patients managed with saline (cf. balanced crystalloids) (Self *et al.* 2018, Semler 2018). Fluids with higher chloride content, such as 0.9% NaCl, have been associated with increased risk of acid-base imbalances and hyperchloraemia when compared to balanced isotonic crystalloids (Raghunathan *et al.* 2014, Krajewski *et al.* 2015). Although these evidence bases in favour of balanced crystalloids are growing, there are studies with neutral results (Young *et al.* 2015, Weiss *et al.* 2017).

In the majority of critically-ill hospitalised patients, it is likely that balanced, more physiological crystalloids with alkalinising effects carry a slight advantage (Drobatz & Cole 2008, Semler 2018). In this study, 89.7% of practices used LRS most frequently, compared to 9.6% favouring saline, in concordance with a recent veterinary study (Hopper *et al.* 2018).

Alongside LRS, Plasmalyte-148 (PL-148) and Normosol-R are also frequently named in veterinary fluid guidelines as appropriate balanced crystalloid solutions to use as replacement fluids (Mazzaferro & Powell 2013). Unlike LRS, which contains lactate as a bicarbonate precursor, both PL-148 and Normosol-R contain acetate and gluconate instead, with a small amount of magnesium instead of calcium. Their osmolality is slightly closer to that of plasma (cf. LRS) and are also considered balanced; they may be recommended in metabolic acidosis due to a slightly alkalinising effect (Weinberg *et al.* 2016). However, PL-148 retails at more than 10 times the price of LRS (£44.20 (PL-148) *versus* £2.80 (LRS) for 500 mL, excluding VAT, from Henry Schein), and Normosol products are not known to be sold by any of the main UK veterinary suppliers. These factors, combined with a lack of familiarity, are likely contributary to why these products have not become more mainstream in the UK, being stocked in only 0.8% of practices.

Hypotonic crystalloid solutions were stocked infrequently, particularly those that are primarily recommended as maintenance fluids such as 0.45% NaCl with 2.5% dextrose, Plasmalyte-56 and Normosol-M (Mazzaferro & Powell 2013). The most frequently stocked hypotonic solution in this study was 0.18% NaCl +4% dextrose which is marketed as a maintenance crystalloid following replenishment of fluid deficits. Maintenance crystalloids typically contain less sodium and more potassium than replacement fluids. The second most popular hypotonic solution, dextrose 5% in water (D5W), is not recommended as a maintenance fluid alone due to risks of in-hospital hyponatraemia (Wang *et al.* 2014), but it can be combined with LRS or saline to make appropriate strength solutions. D5W is most commonly used for delivery of free water in cases of severe hypernatraemia (Mazzaferro & Powell 2013). D5W was stocked by 9.3% of practices, however, those practices which did not stock D5W may make it up themselves when required, using intravenous glucose and sterile water for injection, which was reported to be stocked in 87.4% of practices.

Twenty-five percent of the responding veterinary practices stocked hypertonic saline, a crystalloid often utilised in the initial management of acute hypovolaemic shock (in patients with normal hydration status), particularly in larger dogs (Mazzaferro & Powell 2013, Shafford *et al.* 2013). HTS is also a first-line treatment option for reduction of intracranial pressure in the management of traumatic brain injuries (TBI), inflammatory CNS disease or intracranial neoplasia (Mangat *et al.* 2015, Carney *et al.* 2017). The other common treatment option in these cases is mannitol (Yozova *et al.* 2017a), stocked by 43.0% of practices. It remains unclear which of these two are superior in the treatment of TBI (Boone *et al.* 2015), however, it would make sense that in patients with both TBI and hypovolaemia, HTS may be more appropriate when hypernatraemia is not an immediate concern. In the current study, 194 of the responding practices reportedly stocked neither product, including seven 24-hour hospitals and one 24-hour referral hospital.

Colloids

The lower stocking frequency of colloids is likely attributable to costs, infrequent indication for their use, familiarity, concerns regarding safety and availability. Overall, Gelofusine proved to be the most frequently stocked SC, followed by HES products (Voluven/Volulyte). The reported stocking of dextrans was surprising as they are the least favoured SC in people and have been associated with negative effects on haemostasis, and risks of anaphylaxis and renal failure (Ertmer *et al.* 2009). Consequently, they are no longer sold in several countries, including the USA and it is unclear whether they are still available in the UK.

The popularity of gelatin-based colloids compared to HES is contrary to trends identified in similar survey studies (Yozova *et al.* 2017b, Hopper *et al.* 2018). One of these studies reported that 85% of the respondents selected HES as their most commonly used SC (c.f. only 4% selecting gelatins) (Yozova *et al.* 2017b). North America was overrepresented in these studies therefore the differences may be regional. Alternatively, this may be a reflection of the declining availability and popularity of HES products due to European Union restrictions on their use due to concern over their safety profile. Multiple human trials have documented increased risk of acute kidney injury, requirement for renal replacement therapy and risk of death when HES are used (Myburgh *et al.* 2012) particularly in the critically ill (Zarychanski *et al.* 2013). Veterinary retrospective studies have found conflicting results in patients receiving HES products as they have been reported to be safe in non-azotaemic patients (Yozova *et al.* 2016, Sigrist *et al.* 2017) but have been associated with an adverse outcome including death or acute kidney injury (Hayes *et al.* 2016). This latter study investigated an older HES product (pentastarch) while newer generations of tetrastarches, such as Voluven and Volulyte, are purported to be more safe due to faster degradation and less tissue accumulation (Brooks *et al.* 2016, Hayes *et al.* 2016). Recent evidence has also

raised concern over gelatin-based colloids due to elevations in urinary biomarkers of AKI when compared to other SCs (Boyd *et al*. 2019).

At this stage, there is insufficient evidence in veterinary species to draw definitive conclusions regarding safety of HES products and further prospective studies are required. Currently, HES products are still available to purchase in the UK, albeit at approximately four times the price of gelatins.(£7.15/£7.90 per 500 mL Gelofusine/Geloplasma 4% cf. £30.32 per 500 mL Voluven 6%, excluding VAT, from Henry Schein)

Blood products

Canine blood products

Canine FFP was the most frequently stocked blood product although its use was not explored in this study. A hospital-based study indicated that FFP was primarily used in the management of coagulopathies in animals (Snow *et al*. 2010).

HSA was more popular than CSA, which was reportedly stocked by one practice. Infrequent stocking may also be related to the relatively high cost of albumin products and risk of immunological reactions, which is often considered to be prohibitive to their use and would parallel the declining use of albumin in people (Yano *et al*. 2019).

Haemoglobin-based oxygen carrying solutions were rarely reported, with six respondents reporting to stock them. It is surprising to hear of practices stocking these products as Oxyglobin® is no longer available. In principle, their lack of a 'blood type', lower disease transmission risk and long shelf-life make them an appealing alternative to pRBCs (Zambelli & Leisewitz 2009). In practice, however, known adverse effects and their short plasma half-life (12-20 hours) has limited their applications. An alternative, investigational haemoglobin-based oxygen carrying solution is occasionally available to people in the USA under an expanded access program, but not in Europe (Hemoglobin Oxygen Therapeutics LLC| 2020) while polynitroxylated-pegylated haemoglobin also remains under active research (Cao *et al*. 2017).

Feline blood products

Only 2.5% of practices, all referral hospitals, stocked feline-specific products (pRBC or plasma). This is likely due to difficulties in the collection and storage of blood products in cats.

Blood product acquisition

Thirty-one percent of practices reported use of a blood bank in the event that the appropriate product was not stocked. This was a more popular choice than using a blood donor from their records. Now that large-scale blood product storage is possible due to the amendment to the 2002 Veterinary Medicine Regulations Act in 2007 (Parliament of the United Kingdom 2007), Pet Blood Bank UK and BSA Animal Blood Bank offer quick delivery of products in the event of an emergency. Prior to the 2007 Veterinary Medicines Regulation Act, veterinarians were only authorised to collect blood for immediate or anticipated use under the Animal (Scientific Procedures) Act (Parliament of the United Kingdom 1986).

Study limitations

The survey was purposefully designed to be completed quickly, by anyone within the veterinary practice that was willing. This maximised the response rate but may have resulted in inaccuracies as responses may have been dependant on recall. We contacted 2994 practices, however, only received responses from 396 individual practices; an overall low response rate. Although Fig. 1 shows that our respondents were, geographically, relatively well-distributed, and we had a variety of practice types included, we cannot guarantee that our included practices are representative of all practices within the UK. Respondents were also asked to self-categorise their practice, rather than using a practice standards scheme. This was intentional in order to maximise responses but may have resulted in inaccuracies. Several practices reported stocking of products such as dextrans and HBOCS which was surprising given recent difficulty in acquisition. While stocking of these products was not clarified, the authors speculate that this could have been reported in error or was not representative of use. Despite the above limitations, it can be reasonably assumed that the products described would correspond well to what is used by the practice. Finally, as with any survey, there is always a degree of error due to misinterpretation of questions. In an attempt to mitigate these errors, duplicate responses were compared and documented to be identical in all but one of 27 duplicates.

In conclusions, crystalloids, namely balanced isotonic solutions, are a mainstay in UK small animal veterinary practices. Colloid usage appears less frequent and gelatin-based products are more routinely stocked than HES. Keeping blood products in stock is not commonplace and blood products are often accessed from pet blood banking services. An awareness of the products that are stocked by small animal practices is imperative in constructing applicable evidence-based guidelines and teaching resources. Further research investigating the decision-making, indications, dosages, and benefits of fluid and blood products are required to generate evidence-based guidelines.

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Conflict of Interest

No conflicts of interest have been declared.

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Supporting Information

The following supporting information is available for this article:

Appendix S1: Supporting information