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Research Article

Melatonin Implant for Treatment of Generalized and Localized Alopecia in Dogs

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ABSTRACT

Background/Aim: Hair loss (alopecia) is a complex phenomenon, that may be exist during the lifetime of the animal. Alopecia is a common, on the other hand frustrating disorder in companion animals. Bacterial, fungal and parasitic infections, allergy/atopy, endocrine disease/imbalances and congenital/genetic disorders of hair growth all might contribute to occurence of alopecia. Given the antioxidant effects for melatonin, it might probably has a role within the skin biology. Available evidence suggested that melatonin is capable of modulating hair growth and several researches indicated its usage against alopecia for dogs, whereas detailed studies regarding its topical or subcutaneous usage are lacking. Therefore the purpose of the present study was to report the retrospective results of subcutaneous slow release melatonin implant for treatment of alopecia due to different etiologies among dogs.

Material, Methods: In a susbset of two major groups of dogs were studied: group I consisted of 5 dogs presented with generalized alopecia; consisting seasonal flank alopecia, demodicosis and atopic dermatitis. Group II consisted of 3 dogs presenting local alopecia (sarcoptic mange). Diagnosis was based on relevant tests for all dogs. Afterwards all dogs underwent subcutaneous melatonin implant for treatment of common clinical sign, alopecia. Clinical recovery following melatonin impant was deemed on hair re-growth and quality of new hair, by clinical scoring.

Results/Conclusion: Complete hair growth was evident in 4 out of 5 dogs involved in group I in 6 to 9 weeks. Prior to treatment all 5 dogs presented alopecic clinical scores as 1, where as after melatonin treatment (on week 10) 4 dogs were annotated as score 3, because of complete hair growth. In other group involving dogs with Sarcoptic mange week 10 scores presented as score 2 or 3, because of partial to complete hair growth. Clinical recovery as deemed by hair regrowth caused by subcutaneous treatment might be practically available. During applications no adverse effect was noticed. It may be suggested that melatonin implant may be safely used in dogs with alopecia due to different etiologies.

Keywords: Melatonin, implant, alopecia, dog

Generalize ve lokal alopesili köpeklerde melatonin implantı tedavisi

ÖZET

Özbilgi/Amaç: Kıl kaybı (alopesi), hayvanın hayatı boyunca herhangi bir dönemde var olabilen kompleks bir fenomendir. Alopesi, hayvanlarda sık görülmekle birlikte yıldırıcı bir bozukluktur. Bakteriyal, fungal, parazitik enfeksiyonlar, alerji/atopi, endokrin bozuklukları/hastalıkları ve kongenital/genetik bozuklukların tamamı gibi kıl büyümesine etki eden durumlar, alopesi oluşumuna neden olabilmektedir. Melatonin'in antioksidan etkisi göz önüne alındığında, muhtemelen deri biyolojisinde rol oynayabilir. Elde edilen bulgular melatoninin kıl büyümesini stimule ettiğini göstermekte ve çeşitli araştırmalar anılan hormonun köpeklerde alopesiye karşı kullanılmasını önermekteyken, topikal veya subkutanöz kullanımına ilişkin çalışmalar eksiktir. Anılan nedenlerden ötürü bu çalışmanın amacı farklı etiyolojik nedenlere bağlı alopesi mevcut köpeklerde sağaltım amacıyla subkutanöz uygulanan yavaş salınımlı melatonin implantının retrospektif sonuçlarını bildirmekti.

Materyal ve Metot: Çalışma 2 ana gruba ayrılan köpeklerde gerçekleştirildi: grup I'de göğüste mevsimsel alopesi, demodikozis ya da atopik dermatitis'e bağlı generalize alopesi saptanan 5 köpek mevcuttu. Grup II'deki 3 köpekte ise lokal alopesi (sarkoptik uyuza bağlı) bulunmaktaydı. Tanı amaca uygun testler kullanılarak konuldu. Sonrasında tüm köpeklere, ortak klinik bulgu olan alopesinin sağaltımı amacıyla subkutanöz melatonin implantı uygulandı. Melatonin implantını takiben meydana gelen klinik iyileşme kılların tekrar büyümesi ve yeni şekillenen kılların klinik skorlaması baz alınarak yapıldı.

Bulgular ve Sonuç: Grup I'deki 5 köpekten 4'ünde belirgin bir şekilde tam kıl büyümesi 6.-9. haftalar arasında gerçekleşti. Sağaltım öncesi 5 köpeğin alopesik klinik skorlaması 1 iken, sağaltım sonrası (10. hafta) ise 5 köpeğin 4'ünde tam kıl büyümesi sebebiyle 3 olarak belirlendi. Sarkoptik uyuzlu köpeklerin oluşturduğu diğer grupta ise 10. haftadaki alopesik klinik skor kısmi ya da tam kıl büyümesinden dolayı 2 ya da 3 idi. Subkutaöz melatonin sağaltımı sonucu kıl büyümesinin klinik iyileşmeyi gösterdiği gibi bu yöntem pratik olarak mümkün olabilmektedir. Uygulama sırasında herhangi bir yan etki saptanmadı. Farklı etiyolojiye sahip alopesili köpeklerde, melatonin implantının güvenle kullanılabileceği söylenebilinir.

Anahtar Kelimeler: Melatonin, implant, alopesi, köpek

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Introduction

Hair loss (alopecia) is a complex phenomenon, presenting because of congenital or genetic disorders, or may exist during the lifetime of the animal (Novak and Meyer, 2009). Hair loss occurring throughout life can be further divided into inflammatory and noninflammatory types (Scott et al., 1995; Novak and Meyer, 2009). Alopecia is a common, on the other hand frustrating disorder in companion animals. Bacterial, fungal and parasitic infections, allergy/atopy, endocrine disease/imbalances and congenital/genetic disorders of hair growth all might contribute to occurence of alopecia (Scott et al., 1995; Rosenbaum, 2001; Thompson, 2014). From the owner side it is a cosmetic concern, probably indicating an underlying external or internal disease process (Scott et al., 1995; Rosenbaum, 2001) . From the veterinary surgeon side, unexplained hair loss in dogs is one of the more challenging conditions (Thompson, 2014). The primary author's (K.U.) interest to canine alopecia and its treatment were arroused following receipt of several unexplained alopecia cases, within the previous years. He has been face to face to several and overestimated cases annually by primay dermatological examination, besides by social media, e-mails and on phone calls, in an attempt to support colleagues.

Given the antioxidant effects for melatonin, it might probably has a role within the skin biology (Fischer et al., 1999; Fischer and Elsner 2001). Although photo-stability of melatonin has been a limiting factor, liquid chromatography–mass spectrometric analysis has proven that the melatonin metabolites could possess significant antioxidant activity (Maharaj et al, 2002). Through the available evidence suggested that melatonin is capable of modulating hair growth (Houssay et al., 1966; Allain and Rougeot, 1980; Slominski et al., 2004, 2005), and several researches indicated its usage against alopecia in alopecia for dogs (Paradis, 1996, 2000; Ferrer, 1998; Cerundolo, 1999; Rachid et al., 2003; Frank et al., 2004), whereas detailed studies regarding its topical or subcutaneous usage are lacking. Therefore the purpose of the present study was to report the retrospective results of subcutaneous slow release melatonin implant for treatment of alopecia due to different etiologies among dogs.

Material and Methods

In a subset of two major groups of dogs were studied: group I consisted of 5 dogs presented with generalized alopecia; consisting 1 German shepherd and 1 Boxer dog with seasonal flank alopecia, 1 Labrador retriever with demodicosis and 2 other dogs (1 each French bulldog and Golden retriever) with atopic dermatitis.

Group II consisted of 3 dogs presenting local alopecia (2 Terrier and 1 Pointer with sarcoptic mange) (Pin et al., 2006; Ural, 2014).

The diagnosis of atopic dermatitis was based through literature search and atopy criteria (Favrot et al., 2010; Olivry, 2010)

Relevant physical examination, routine haematology, serum biochemistry and coagulation tests were performed (excessive data not shown). All clinical records from late February to July 2015 were searched to identify clinical cases for which a D-dimer test had been performed.

In dogs with evidence of Demodicosis or sarcoptic mange, the diagnosis was based on clinical signs compatible with demodicosis (Ural, 2014) or sarcoptic acariasis (Deger and Ural, 2013; Ural, 2014), respectively, and skin scrapings.

Clinical evaluation

Clinical recovery following melatonin impant was deemed on hair re-growth and quality of new hair, as was previously described (Frank et al., 2004). A clinical scoring was practically available as;

Score 1: no hair regrowth (the percentage of body area involving alopecic lesions affected were unchanged);

Score 2-3; partial hair re-growth (the percentage of body area involving alopecic lesions affected decreased);

Score 2-3; complete hair re-growth (< 25% of the body area remained affected) (Frank et al., 2004).

Treatment procedure

All cases were treated with a subcutaneous sterile implant containing 18 mg melatonin (Regulin implant; Ceva Hayvan Sağlığı A.Ş., Ceva Santé Animale, France) placed in the thoracolumbar or interscapular areas by use of a single-use weapon implanter according to the manufacturer's instructions. On each application twice 18 mg melatonin was implanted once weekly for a total of 4 applications. In addition to melatonin treatment dogs with sarcoptic mange and demodicosis received 0.6 mg/kg eprinomectin (Eprinex pour-on, Topkim) topically for 4 occasions.

Results

Complete hair growth was evident in 4 out of 5 dogs involved in group I in 6 to 9 weeks (Fig. 1-6). Prior to treatment all 5 dogs presented alopecic clinical scores as 1, where as after melatonin treatment (on week 10) 4 dogs were annotated as score 3, because of complete hair growth. In other group involving dogs with Sarcoptic mange week 10 scores presented as score 2 or 3, because of partial to complete hair growth.

Discussion

Canine recurrent flank alopecia (CRFA) (with synonyms i.e. seasonal growth hormone deficiency, seasonal flank alopecia, cyclic follicular dysphasia, canine idiopathic cyclic flank alopecia, and follicular dysphasia) is a recently known skin diseases with an unknown cause. It is frequently observed in Airedale terriers, Boxers and bulldogs, besides in several other breeds and characterized by episodes of truncal hair loss, existing on recurrent basis (Paradis, 2000). As seen in our cases the disorder was noticed on a recurrent basis. CRFA is characterized by a nonscarring alopecia, usually bilaterally symmetrical (Paradis, 2000). In our CRFA cases lesions were symmetrical, which gave respond to melatonin treatment. On 2 cases hair loss was not evident after weeks 4, as hair regrowth was noticed.

In canine pattern baldness, a common condition affecting short coated dog breeds with acquired alopecia in specific body regions (Paradis, 2000), oral melatonin treatment at a dose of 5 mg once daily for 30 days may promote hair growth (Paradis, 1996, 2000). In another inherited skin condition such as Follicular dysplasia (Ferrer, 1998; Cerundolo, 1999) oral 3 mg melatonin twice daily administration of melatonin may help hastening hair regrowth (Rachid et al., 2003).

Melatonin, is a neurohormone secreted within the pineal gland during darkness in mammals (Chemineau et al., 1996; Reiter et al., 2002; Tan et al., 2002; Rodriguez et al., 2004). Currently it may be safely suggested that melatonin is capable of modulating hair growth (Allain and Rougeot, 1980; Houssay et al., 1966; Slominski et al., 2004, 2005). The prolonged and slow release of melatonin by a subcutaneous implant (for 4 weekly

application), as described here, allowed to mimic short days while the present cases eye perceive long periods of summer and spring, similarly to a prior report in sheep (Chemineau et al., 1996). The potential influence of subcutaneous melatonin within the treatment of primary or secondary skin lesions such as alopecia may be briefly discussed.

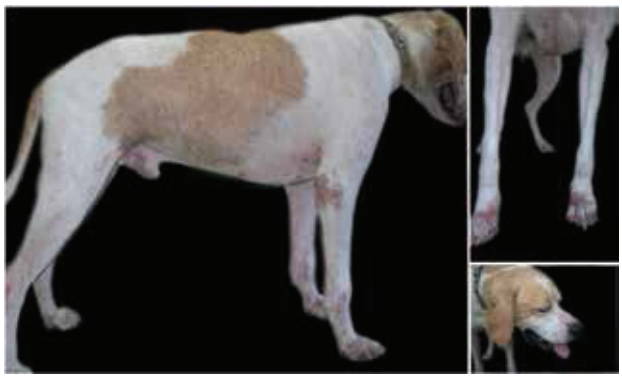

Figure 1. Demodicosis was evident on initial submission. Photographic record was at admission to the clinic, prior to melatonin implant

Şekil 1. Başlangıç muayenesinde demodikozis mevcut. Fotoğraf kaydı kliniğe getirildiğinde, melatonin implantından hemen once.

Figure 2. Clinical recovery and complete hair growth following melatonin + eprinomectin implant therapy on week 6.

Şekil 2. Melatonin + eprinomektin implant sağaltımını takiben 6. haftada klinik iyileşme ve tam kıl büyümesi.

Figure 3. Seasonal flank alopecia (mainly hair loss) in a German Shepherd dog.

Şekil 3. Alman Çoban Köpeğinde mevsimsel göğüs alopesisi (esas olarak tüy kayıbı).

Figure. 4. Application of subcutaneous melatonin implant via special implant weapon thorugh interscpular area in to the case as shown in Fig 3.

Şekil 4. Şekil 3'te gösterilen olguda subkutanöz melatonin implantının özel implant tabancası ile direkt olarak interscapular bölgeye uygulanması.

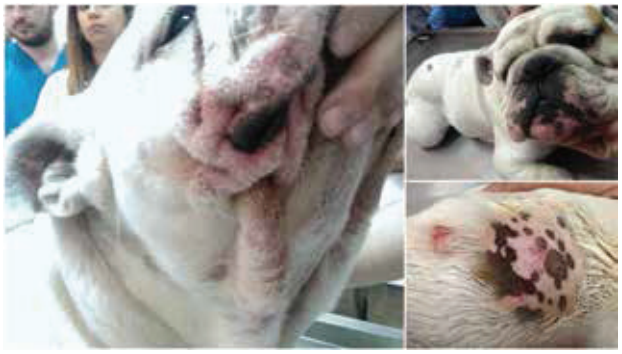

Figure 5. Atopic dermatitis in a bulldog.

Şekil 5. Bulldog'da atopic dermatitis.

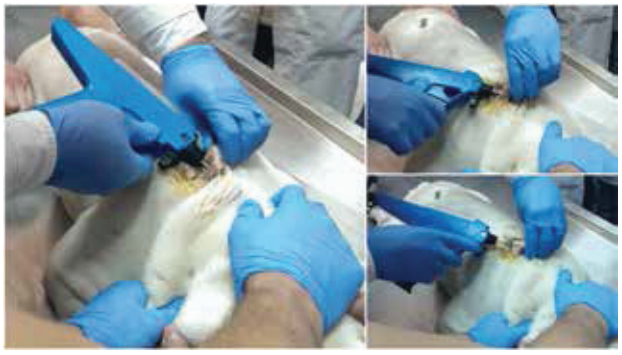

Figure 6. Application of subcutaneous melatonin implant via special implant weapon thorugh thoracolumbar area in to the case as shown in Fig 5.

Şekil 6. Şekil 5'de gösterilen olguda subkutanöz melatonin implantının özel implant tabancası ile direkt olarak thorakolumbar bölgeye uygulanması.

A frequent question that the present authors usually face to face is that, natural sources of melatonin or remedies. Melatonin is naturally exist in some of the plants. Indeed, for absorption of 3 mg of melatonin, which is a frequently used therapeutic dose for dogs underweighing 10 kg, 120 bananas or 30 large bowls of rice (Paradis, 2000) have to be consumed! Melatonin is capable of easily synthesized, thus a relatively cheap hormone. It may be used orally or systemically using aqueous SC injections (in which to the present authors' knowledge not available in veterinary practice in Turkey) or slow-release SC implants (Paradis, 2000). As afromentioned

above melatonin was administered as a slow release weekly implant for 4 applications

Contrarily standardization of melatonin could be problematic, causing varying drug content in the compound, alternating bioavailability and absorption (Frank et al., 2004). For those reasons oral melatonin treatment should be used with caution changing therapy protocole and duration. This may be the reason for choice of subcutaneous implant and controlled release in the present cases. Furthermore timing of melatonin administration for oral route is challenging. In sheep and ponies oral melatonin was used following 8 hours of daylight the evening or in preceding nightfall for mimicking a shortened daylength (Kennaway et al., 1982; Argo et al., 1991; Pawlikowski et al., 2002).

Melatonin may attenuate lipid peroxidation via antioxidative activity, suggesting that it may be capable of protecting skin integrity through maintainence of a functional epidermal barrier (Kilanczyk and Bryszewska, 2003) and antiapoptotic effects (Fischer et al., 2006).

Melatonin, as discovered by Lerner (Lerner et al., 1958, 1960) possesses pleiotropic bioactivities such as immunomodulator etc. (Yu and Reiter, 1993; Wiesenberg et al., 1998; Carlberg, 2000; Dubocovich et al., 2003; Reiter, 2003). Furthermore, as was also aforementioned above, function as a free-radical scavenger, broad-spectrum antioxidant, and protective (against oxidative stress) (Reiter et al., 2002; Tan et al., 2002; Rodriguez et al., 2004). Taking into account, melatonin presents several features that might be useful for a stress-response system belonging to the skin (Slominski et al., 2005a). Melatonin has been experimentally induced hair growth, fur pigmentation (Maestroni et al., 1998; Bartsch et al., 2002; Slominski et al., 2004, 2005a, 2005b). As melatonin receptors are well expressed in skin, they mediate phenotypic actions regarding cellular proliferation and differentiation.

Melatonin treatment resulted within partial to complete hair re-growth in 62% of dogs with Alopecia X (Frank et al., 2004). In that study not all of the cases with Alopecia X re-grew hair despite melatonin treatment. Proposed explanations included dosage error and poor absorption of the compound. Melatonin is in nutraceutical class, though standardization of the product is problematic, resulting in alternating drug content in the preparation, changable bioavailability and absorption (Frank et al., 2004). Therefore in the present authors' experience oral melatonin treatment should be used with caution on drug concentration, influencing therapy protocole and duration. This may be the reason for choice of subcutaneous implant and controlled release in the present case. The major flaw in the present case report was that serum melatonin concentrations were not measured. Another relevant factor is that the timing of melatonin administration for oral route is challenging. In researches with humans, sheep and ponies oral melatonin was administered in the evening preceding nightfall or following 8 hours of daylight in an attempt to mimic a shortened daylength (Kennaway et al., 1982; Argo et al., 1991; Pawlikowski et al., 2002). In the present study subcutaneous implant excluded the timing caution for drug administration.

Clinical recovery as deemed by hair regrowth caused by subcutaneous treatment might be practically available. During applications no adverse effect was noticed. It may be suggested that melatonin implant may be safely used in dogs with alopecia due to different etiologies.

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