Title

Topical propranolol for infantile haemangiomas: A systematic review

Running head

Topical propranolol for infantile haemangiomas

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Conflict of interest

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Abstract

Infantile haemangiomas are the most common tumour of infancy. Whilst the majority are left untreated to involute spontaneously, residual skin changes commonly occur, particularly in superficial haemangiomas. The current first line treatment for problematic lesions is oral propranolol, however due to the risk of systemic adverse effects, the use of off-label topical preparations has recently been investigated. Our systematic review was conducted in accordance with PRISMA guidelines. Four databases were searched to identify original articles evaluating the use of topical propranolol as the primary therapy for infantile haemangiomas. Twelve articles with a total of 597 patients and 632 haemangiomas were included. Three topical propranolol preparations were used, creams, ointments and gels, and were all prepared by local pharmaceutical laboratories. The concentration of propranolol ranged from 0.5% to 5%. Treatment duration ranged from two weeks to 16.5 months. Overall, 90% of lesions improved following the initiation of topical propranolol. A good or excellent response, defined as a reduction in size of at least 50%, was seen in 59% of lesions. Earlier initiation of treatment (less than 3 months of age) was associated with improved outcomes. No systemic adverse effects were reported. Minor local reactions were seen in 1.3% of patients. Topical propranolol is safer than oral propranolol, though may be less effective. Topical propranolol may be more suitable for patients with small, superficial haemangiomas at risk of cosmetic sequelae, where the cosmetic or symptomatic impact does not warrant oral propranolol treatment.

Introduction

Infantile haemangiomas are the most common tumours of infancy. They are benign vascular neoplasms with an incidence of 4-10%[1,2]. They are more common in female, Caucasian and low-birth weight infants[3]. The lesions are rarely detectable at birth but become evident during a proliferative phase after four weeks[3] and continue to grow rapidly until a mean age of 3.2 months[4]. Rapid vasculogenesis and angiogenesis are followed by spontaneous involution beginning at around one year of age[4]. Fifty percent spontaneously regress by age 5 years, 70% by age 7 years[5]. Infantile haemangiomas may be classified according to their depth; superficial, located in the upper dermis (and therefore visible on the skin), deep, extending to subcutaneous fascia, or mixed[3]. They can occur anywhere on the body but are most commonly found on the head and neck[3]. The diagnosis of infantile haemangiomas is clinical. There are various scoring systems that can be used to assess severity and complications, such as the Haemangioma Severity Scale[6]. Treatment outcomes can be evaluated using scoring systems based on changes in colour, texture and volume, for example the Achauer system, which grades reduction in lesion size as poor (0-25%), fair (26-50%), good (51-75) or excellent (76-100%)[7].

Ulceration is the most common complication of infantile haemangiomas, with an incidence of up to 16% in patients referred to tertiary centres[8]. Peri-orbital haemangiomas can lead to visual impairment whilst paraglottic or tracheal lesions can cause life-threatening airway obstruction[6]. Facial haemangiomas, particularly around the nose and lip, can cause permanent disfigurement[6]. Due to the risk of complications, 10-15% of infantile haemangiomas require treatment[9]. The majority of haemangiomas are left untreated to involute spontaneously but residual skin changes such as telangiectasia, fibrofatty tissue and skin laxity commonly occur, particularly in superficial haemangiomas[6,10]. Previously, corticosteroids were the treatment of choice, with alternatives such as interferon-alpha and vincristine[9]. The beneficial effect of oral propranolol on infantile haemangiomas was discovered incidentally in 2008[11]. Its mechanism of action is not fully understood, but may be

due to inhibition of angiogenesis, pericyte-mediated vasoconstriction, induction of endothelial cell apoptosis and/or inactivation of the renin-angiotensin system[12]. Due its superior efficacy compared to the aforementioned medications, oral propranolol is now considered first line[13]. Oral propranolol administration carries the risk of systemic effects such as hypoglycaemia, bradycardia, hypotension, bronchospasm and electrolyte disturbance, and close monitoring (which may involve hospital admission) is required during treatment initiation[13]. Adverse effects have been reported to occur in 31% of patients treated with oral propranolol at the empirical cardiovascular dose, although commonly these are sleep disturbance and acrocyanosis; serious adverse effects are much rarer[13,14]. Lower dose oral propranolol has been shown to cause fewer adverse effects[15].

Localised methods of drug delivery, including topical and intralesional application, have been investigated and trialled. The 2015 recommendations from the European expert group state that as there is insufficient information regarding the safety and efficacy of topical betablockers (which are currently off-label), they cannot be recommended as standard treatment, but they have a potential for future use in small, superficial haemangiomas[13]. Topical application allows drug delivery directly to the diseased area, avoiding first pass metabolism. It has been suggested that topical propranolol acts to suppress haemangioma proliferation by reducing the levels of vascular endothelial growth factor (VEGF)[16]. For superficial haemangiomas, which do not extend beyond the papillary dermis, the local accumulation of propranolol without significant systemic absorption may be an advantage[17]. The optimal preparation, dosage and duration of topical propranolol are currently unknown. The aim of this systematic review is to assess the efficacy and safety of topical propranolol in the treatment of infantile haemangiomas.

Methods

Search strategy

The review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') pro forma (Fig. 1). Four databases were searched; EMBASE (1947 – present), MEDLINE (1946 – March week 3 2017), PubMed (1966-present) and Cochrane Library (March 2017). The search terms were split into three categories and combined using "AND", individual search terms performed within each category were combined using "OR". The first category included "adrenergic beta-antagonist", "beta-antagonist", "beta blocker" and "propranolol". The second category contained "haemangioma", "hemangioma" and "vascular malformation". The third category contained "topical" and "transdermal". The search was up to date as of March 2017.

Inclusion and Exclusion Criteria

Original articles evaluating topical propranolol as the primary therapy for treating infantile haemangiomas were included. Articles written in a foreign language were only included if a suitable translation was found. Articles not reporting a clinical outcome were excluded. Meta-analyses, review articles, case studies, non-human studies and small studies (with fewer than five patients) were excluded.

Data Collection

Three authors (A.P., S.R. and R.M.) independently reviewed the articles identified. Articles were screened by title and abstract and those deemed relevant were reviewed in full text and selected or rejected based on the inclusion and exclusion criteria. Data extraction was performed by two authors (A.P. and S.R.) and compiled and analysed in Microsoft Excel®. This included the number of patients, patient demographics, the site and size of the haemangioma, the preparation, concentration and dosing of propranolol, the duration of treatment, the method of measuring response, the response rate, the number of patients with rebound after cessation of treatment and any adverse effects. Overall response rate was defined as the

percentage of lesions showing improvement with treatment. A good or excellent response was defined as the percentage of lesions with a more than 50% reduction in size, as specified by the Achauer system[7]. Where possible, data was combined to find overall values, however not all articles included data on all of these measures.

Results

Database searching identified 454 articles, and one article was identified from a reference list (Fig. 1). Subsequently 54 articles were assessed in full text. After inclusion and exclusion criteria were applied, 12 articles with a total of 597 patients and 632 haemangiomas were selected for review (Table 1).

Insert Figure 1.

Patient characteristics

65% of patients were female. The age at treatment initiation ranged from 3 weeks to 33 months, with a mean of 4.5 months. Three studies included patients with mixed (n=30) or deep (n=6) haemangiomas, eight studies involved superficial haemangiomas and one study did not specify the depth. The lesions were located all over the body, including the head and neck and anogenital region. The haemangioma size ranged from 0.5cm^2 to over 10cm^2.

Treatment regimen

Three topical propranolol preparations were used, creams, ointments and gels, all prepared by local pharmaceutical laboratories. Propranolol concentrations ranged from 0.5% to 5% (Table 1). In seven out of twelve studies, treatment was stopped under the following circumstances; disappearance of the lesion, no response to treatment, appearance of a deep component or adverse effects. In these instances, treatment duration ranged from two weeks to 16.5 months (Table 1). The remaining five studies specified treatment durations, ranging from 2 weeks to 10 months.

Five studies performed pre-treatment screening including echocardiography, electrocardiography, blood pressure, liver and kidney function tests and blood glucose levels. Five studies treated patients in hospital for the first 24 - 48 hours and monitored vital signs and blood glucose levels before and after topical application.

Insert Table 1.

Evaluating response to treatment

All studies used clinicians to evaluate the treatment response, the number of clinicians involved was not specified. Seven studies used photography to document the response and change in size and two used Doppler ultrasonography. The Achauer grading system (n=3) or similar method (n=6) where the grade of response (poor, moderate, good or excellent) was determined by the percentage reduction in size were used to measure response. Three studies used a haemangioma score that took into account colour, consistency and size.

Reduction in haemangioma size

Across all studies, an improvement in 90% of haemangiomas was seen at the end of the treatment period (543 out of 602 lesions – 30 lost to follow-up). Ten studies (389 lesions) specified a reduction in size of at least 50% (a good or excellent response). This was seen in 59% of lesions (n=228). The overall response rate ranged from 67% to 100%. The good or excellent response rate ranged from 42% to 86%. The highest good or excellent response rate of 86% was obtained using a 0.5% nano-propranolol hydrogel applied three times daily until 90% of the lesion had disappeared (for up to 11 months). In this study, propranolol was incorporated into nanoparticles of colloidal silicon dioxide with the aim of increasing skin penetration[18]. The lowest response rate of 42% was obtained using a 3% propranolol gel applied three times a day for three months[16].

Speed of response

Five studies investigated the onset of treatment response. Within the first month of treatment, fading, softening and early regression was noted. In patients with a size reduction of over 50%, change in colour from red to purple and softening of the lesion was seen within 7 days of treatment initiation, and this was followed by a progressive reduction in size[17].

Optimum dosage of propranolol

The application frequency and concentration of propranolol did not affect outcome (Figs 2-3). When topical propranolol was applied twice a day, the overall response rate was 91% (range 66-100%) and 55% (range 44-75%) of lesions had a good or excellent response . For three times daily applications, the overall response and good or excellent response rates were 89% (range 81-95%) and 62% (range 42-86%) respectively. No studies directly compared the frequency of application. One study did not identify a significant difference between 2.5% and 5% propranolol gel, both were better than placebo[17].

Insert Figure 2.

Insert Figure 3.

Rebound growth

Six studies (508 patients) reported the occurrence of rebound growth, which occurred in 1.2% (n=6) up to five months after cessation of treatment. The characteristics of the lesions that exhibited rebound growth were not specified in the studies.

Adverse effects

In the eleven studies (600 patients) that documented adverse effects, no systemic effects attributable to topical propranolol were recorded. Minor localised side effects, such as itching and erythema, were seen in 1.3% (n=8) (Table 2). Two studies included low-weight preterm infants who did not experience an increased complication rate or any systemic side effects[19,20].

Insert Table 2.

Oral, topical and intralesional propranolol

One study compared oral (n=15), topical (n=15) and intralesional propranolol (n=15)[21]. A higher proportion of haemangiomas improved with oral compared to

topical and intralesional treatment (86.7% *vs.* 66.7% and 53.3% respectively)[21]. The response was faster in the oral group, with an initial response seen in 2-4 weeks (mean 2.67 weeks) compared to 3-8 weeks (mean 5.87 weeks) in the topical group. Treatment duration was shorter in the oral group compared to the topical group (3-9 months, mean 5.13 months, *vs.* 5-10 months, mean 7.47 months)[21]. In the oral group, one patient suffered a syncopal attack and 3 patients had a significantly lower heart rate and diastolic blood pressure. No systemic effects were observed with topical treatment[21].

Depth of lesion and treatment initiation

A better response for superficial compared to mixed or deep haemangiomas was seen in one study[22]. Two studies found an improved response when treatment was initiated earlier[19,23]. One study achieved an excellent response in 52% of patients aged between 3-9 weeks at treatment initiation, compared to 33% aged 10-20 weeks and 0% aged 22-52 weeks[23].

Discussion

Oral propranolol is currently the first line treatment for infantile haemangiomas[13], but alternative, topical beta-blocker treatments are being explored. We identified 12 studies published between 2012 and 2017 in which topical propranolol was the primary treatment for infantile haemangiomas in over 600 patients, with no reported systemic side effects. Overall, 90% of lesions improved following the initiation of topical propranolol. A good or excellent response was seen in 59% of lesions. Other studies have shown that patients treated with oral propranolol had a response rate of 98%[14]. In patients with small, superficial haemangiomas, the risks of systemic treatment with oral propranolol may outweigh the benefits. Retrospective studies of untreated haemangiomas have demonstrated high rates of cosmetic sequelae[10,24]. A lower risk, less efficacious treatment with topical propranolol may therefore be a good option in these cases.

Treatment response, regimens and rebound

Superficial haemangiomas responded well to treatment unlike mixed or deep haemangiomas[22,23]. The size of the lesion did not affect the outcome.[20,25,26] One study reported that larger lesions (median 3cm^2) had better outcomes compared to a smaller lesion group (median 1cm^2)[27]; the authors theorised that reduced surface interface area of small lesions led to decreased topical efficacy[27]. Starting topical propranolol treatment early (under 3 months of age) was shown to improve response rates[19,23,25].

Heterogeneous concentrations and preparations were used in each study, making comparisons between them difficult, however there was no evidence to suggest that higher concentration preparations improved response rates[17]. The duration of treatment varied, some studies reporting outcomes as early as 2 weeks and others continuing treatment until the desired effect was achieved (up to 16.5 months). This could in part explain the varying response rates seen in different studies. Compared

to oral propranolol, topical treatment may need to be continued for longer in order to achieve the same effect[21].

Rebound growth was observed in 1.2% of cases and up to five months after the cessation of treatment. This figure may be unreliable as not all studies continued follow-up after treatment was stopped or for sufficient lengths of time (less than five months).

Measuring response

The method of measuring response was variable and grading was largely subjective introducing the potential for bias and complicating the definition of efficacy. The outcome measures were often subjective, and although similar, did not follow a standardised approach. Pooling data to obtain an overall response rate may therefore be misleading.

Adverse effects

Our review of 600 patients found topical propranolol to be a safe and effective treatment for infantile haemangiomas with no reported systemic side effects. Although high concentrations of topical propranolol are absorbed and retained by the skin[28], when serum levels of propranolol were measured after topical application in 20 infants, they were always below the measureable range (<20ng/mL, therapeutic range 50-300ng/mL)[20]. This could explain why the low systemic adverse effect profile was encountered.

Oral propranolol and other beta blockers

Oral propranolol has increased efficacy and works faster than topical propranolol[21], it also has an increased incidence of systemic adverse effects[14]. In vivo animal studies comparing the concentration-time profiles in the dermis for oral *vs.* topically applied propranolol found that the peak concentration was over 300 times higher following topical administration[17]. In addition, orally administered propranolol was eliminated from the skin quickly[17]. In vitro and in vivo human studies have shown that a much smaller proportion of topical propranolol is absorbed into the

bloodstream[28,29]. The increased efficacy of oral *vs.* topical propranolol could be explained by a combination of local and systemic mechanisms of action.

Due to the availability of topical timolol, a common ophthalmic solution, more studies have reported on the use of topical timolol instead of topical propranolol[30–32]. A meta-analysis identified an 83% response rate in superficial infantile haemangiomas treated with topical timolol[33]. Sleep disturbance and symptomatic bradycardia following initiation were the only reported systemic adverse effects in three patients[33,34]. In vitro analysis of the permeation of beta-blockers through the human epidermal membrane revealed that propranolol was ten times more permeable than timolol[35]. Whilst this is therapeutically advantageous, it may increase the risk of localised adverse effects.

Limitations

The high number of variables between studies makes reliable comparisons difficult. There is a lack of standardisation in the treatment regimes, with significant variability in the preparation and dosing. The age at treatment initiation could have affected the outcomes, as earlier treatment initiation was associated with improved outcomes. Most of the included studies were cohort studies. Of the two randomised trials[17,21], only one included a placebo-controlled group[17], which is particularly important as infantile haemangiomas are known to involute spontaneously.

Future Trials

There is a need for high quality randomised control trials to establish the viability of topical propranolol for the treatment of infantile haemangiomas. We suggest a focus on patients with small, superficial haemangiomas who would otherwise be untreated leaving the possibility of lifelong scarring or skin discolouration. As no benefit was found with three times daily application or higher concentration preparations, a twice daily application of a lower dose, e.g. 2%, would seem appropriate initially. Once the benefit of topical propranolol *vs.* placebo has been established, the preparation, dosing and treatment regimen could be analysed in comparative trials.

Conclusions

Topical propranolol is a treatment option for infantile haemangiomas and preliminary evidence suggests that it is effective and safe. It may be particularly useful in patients with small superficial haemangiomas, where the cosmetic or symptomatic impact does not warrant oral propranolol treatment.

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Table 1.

Study	Preparation	Dose	Frequency	Duration	% of lesions with improvement	% of lesions with good or excellent response
Kunzi-Rapp 2012[19] Prospective cohort	1% propranolol ointment	Thin layer – around 15µg propranolol / cm^2	Twice daily	Up to 16.5 months	91% (n=59/65)	Not specified
Wang et al. 2012[22] Prospective cohort	3% propranolol gel	Not specified	Three times daily	1 – 10 months	92% (n=47/51)	57% (n=29/51)
Xu et al. 2012[25] Retrospective cohort	1% propranolol ointment	Dependant on size of lesion	Three times daily	5 – 59 weeks, average 21 weeks	90% (n=25/28)	57% (n=16/28)
Bonifazi et al. 2013[23] Prospective cohort	1% propranolol cream	Maximum daily dose not exceeding 2mg/kg	Twice daily	4 – 6 months	81% (n=48/59)*	44% (n=26/59)
Zaher et al. 2013[21] Randomised single-blind trial	1% propranolol ointment	Not specified	Twice daily	5 – 10 months, average 7.5 months	67% (n=10/15)	53% (n=8/15)
Kovačević et al. 2014[36] Retrospective cohort	1% propranolol cream	Not specified	Twice daily	10 months	100% (n=8/8)	75% (n=6/8)
Schneider et al. 2014[20] Retrospective cohort	1% propranolol gel	1-2mm layer under occlusive dressing for 2 hours	Twice daily	12 weeks	99% (n=147/148)	Not specified
Chen et al. 2015[37] Retrospective cohort	0.5% nano-propranolol hydrogel	2ml / cm^2	Three times daily	2 weeks – 11 months	86% (n=43/50)	86% (n=43/50)
Tang et al. 2015[16] Prospective cohort	3% propranolol gel	Not specified	Three times daily	3 months	82% (n=27/33)	42% (n=14/33)
Zhou et al. 2014[17] Randomised double-blind placebo-controlled trial	2.5% and 5% propranolol gels	2mg / cm^2 for 2.5% gel or 4mg / cm^2 for 5% gel	Twice daily	2 weeks	2.5% group: 100% (n=15/15) 5% group: 93% (n=14/15)	2.5% group: 60% (n=9/15) 5% group: 73% (n=11/15)
Mashiah et al. 2017[27] Retrospective cohort	4% propranolol gel	For lesion size of 5cm^2 – 6mg propranolol	Twice daily	3 – 16 months (mean 8 months)	83% (n=62/75)	57% (n=43/75)
Wang et al. 2017[26] Prospective cohort	2% propranolol cream	Not specified	Three times daily	Until the lesion disappeared or 8 months	95% (n=38/40)	58% (n=23/40)

*30 patients lost to follow-up.

Table 2.

Study	Adverse effect	Number of patients	Propranolol preparation	Management
Wang et al. 2012 [22]	Redness	3	3% propranolol gel three times daily	Resolved spontaneously
Kunzi-Rapp 2012 [19]	Itching	1	1% propranolol ointment twice daily	Not specified
Chen et al. 2015 [37]	Itching	2	0.5% nano-propranolol hydrogel twice daily	None
Mashiah et al. 2017 [27]	Irritation and redness	2	4% propranolol gel twice daily	Not specified

Legends

Figure 1: Summary of the article selection process.

Figure 2: The response rate for different frequencies of application of topical propranolol (pooled data). A good or excellent response rate was defined as a reduction in size of over 50%. (BD – twice a day, TDS – three times a day)

Figure 3: The response rate for different concentrations of topical propranolol (pooled data). A good or excellent response rate was defined as a reduction in size of over 50%.

Table 1: Propranolol preparation, administration and response rate. A good or excellent response was defined as more than a 50% reduction in haemangioma size.

Table 2: Adverse effects.

Figure 1.

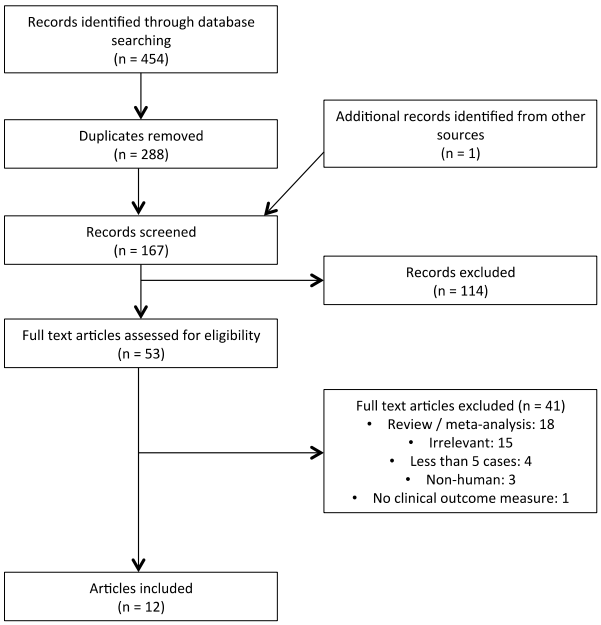

Records identified through database searching
(n = 454)
Duplicates removed
(n = 288)
Additional records identified from other sources
(n = 1)
Records screened
(n = 167)
Records excluded
(n = 114)
Full text articles assessed for eligibility
(n = 53)
Full text articles excluded (n = 41)
• Review / meta-analysis: 18
• Irrelevant: 15
• Less than 5 cases: 4
• Non-human: 3
• No clinical outcome measure: 1
Articles included
(n = 12)

Figure 2.

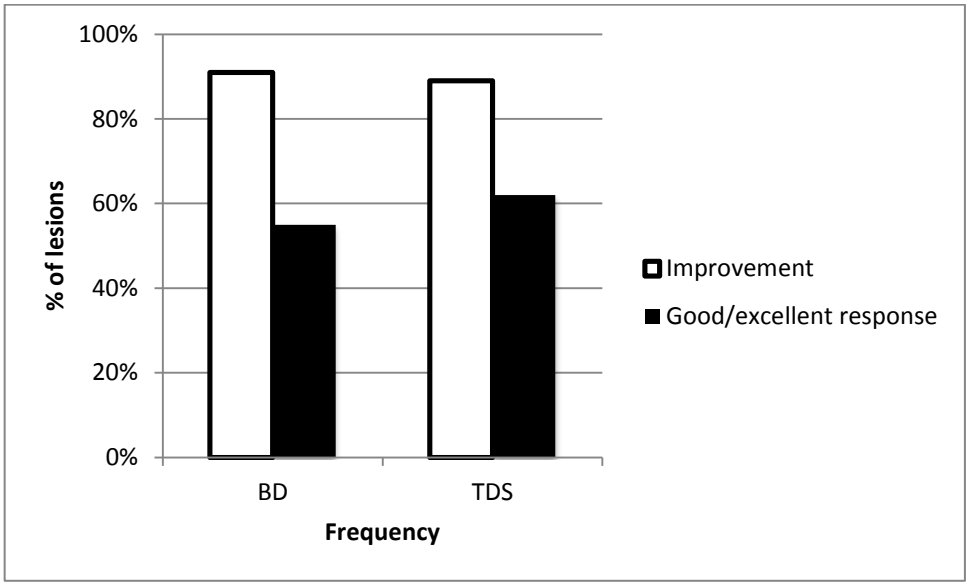
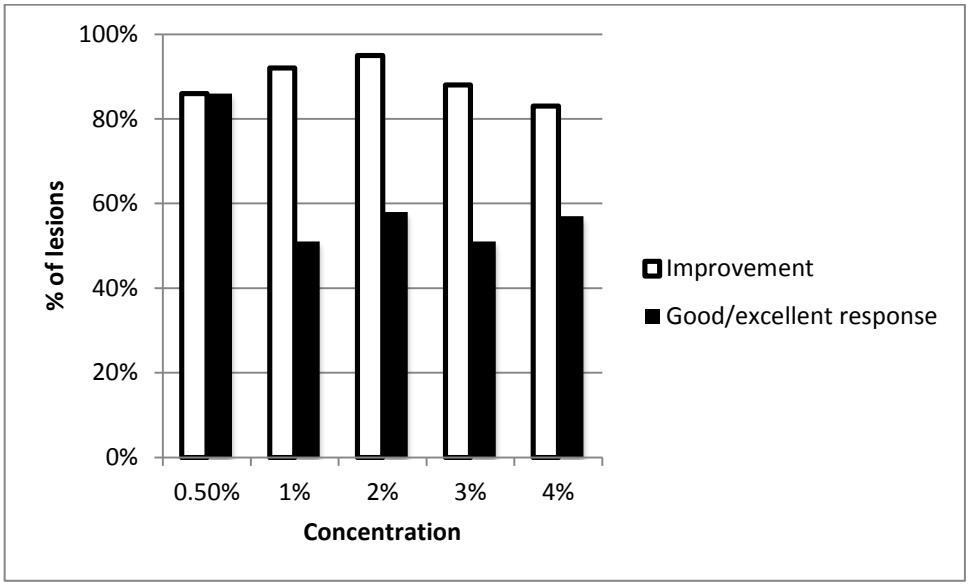

100%
80%
60%
40%
20%
0%
% of lesions
BD
TDS
Frequency
Improvement
Good/excellent response

Figure 3.


100%
80%
60%
40%
20%
0%
% of lesions
0.50%
1%
2%
3%
4%
Concentration
Improvement
Good/excellent response