



## Estimation Of Substance P Level In Normal Pulpal Condition Compared To Pulpal And Periapical Diseases

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### ABSTRACT

**Introduction:** Pulp can be inflamed due to physiologic, pathogenic or iatrogenic factors. The stimulation of the peripheral nerve ending in the pulp causes the release of neuropeptides such as Substance P, Calcitonin Gene Receptor Peptide (CGRP), Neurokinin A and Neurokinin B. These neuropeptides mediate neurogenic inflammation. Substance P is the first neuropeptide to be isolated in the dental pulp and is reported to be associated with the pulpal pain experienced by the patient.

**Aim:** To Determine and compare the level of Substance P in diseased pulpal conditions and healthy pulpal conditions.

**Materials and Method:** The search was performed in various electronic databases (i.e. Pubmed Central, Scencedirect, Cochrane, Web Of Science and Lilac) till 1,February 2022. Studies were selected if it compared the level of Substance P in diseased and healthy pulpal conditions.

**Results:** Search from the database showed 67 studies out of which 5 studies were included for the systematic review based on the inclusion criteria. The level of SP was measured either in GCF, pulp tissue, root canal exudate or saliva. There was a statistically significant increase in Substance P level in teeth with diseased pulpal conditions.

**Conclusion:** SP, NKA, and CGRP are eminent neurotransmitters in the propagation of moderate to severe pain signals and are increased in case of pupal disease. Substance P is significantly increased in diseased pulpal conditions when compared to healthy and intact teeth.

**Keywords:** *Substance P, Pulp, Irreversible pulpitis, CGRP, neuropeptides, Pulpal inflammation, Medical, Health*

### INTRODUCTION

Odontogenic pain is the pain that originates from the teeth and its supporting tissues(1)(2,3)(1). Dental pulp is abundantly innervated with sensory nerve fibres originating from the trigeminal ganglion(4).

Nociceptive fibers are prevalent in the trigeminal nerve that innervate the pulpal and periapical tissues(5)(6–9)(5). Dental pulp can be inflamed due to various factors such as anatomic, pathological

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or iatrogenic conditions(10,11)(12,13)(10,11). The inflammation can occur due to direct stimulation of the nerve endings or indirectly due to the release of chemical mediators that act on the nerve endings. Inflammation of the dental pulp is perceived as pain or altered pain response.

Stimulation of the sensory neurons causes the release of neuropeptides such as Substance P(SP), Calcitonin Gene Receptor Peptide(CGRP), Neurokinin A and B (NKA, NKB)(14)(15,16)(14). Neurogenic inflammation of the dental pulp is attributed to the release of neuropeptides and controls the blood flow and regulates inflammation and repair. Substance P is the first neuropeptide to be isolated from the dental pulp. SP is primarily localized in the trigeminal ganglion and dorsal root ganglion(17,18)(19,20)(17,18).

The goal of endodontic procedures is to eliminate pain associated with inflamed pulp and periapical tissues(21)(22,23)(21) . The pain in pulpitis can range from mild to severe(24)(25)(24). Pain can be spontaneous or intermittent. Hence, pain management before, during and after endodontic therapy becomes extremely important(26)(27–30)(26)(31)(32,33)(31). Substance P can be used as a biological marker to diagnose the inflammatory condition of the pulp and correlate the pain experienced by the patient.

## MATERIALS AND METHOD

The study was conducted in accordance with the Preferred Reporting Items of Systematic Review and Meta Analysis Protocols (PRISMA) guidelines.

### *Structured Question*

Is there reduction in the level of Substance P after endodontic procedures in pulpal diseases?

### *Pico Analysis*

POPULATION - Substance P in teeth with pulpal diseases

COMPARISON - Substance P in healthy teeth

OUTCOME- Level of Substance P

### *Inclusion criteria*

Prospective clinical trials in which endodontic procedures are performed and substance P level is measured in saliva or GCF or pulp or root canal exudate using ELISA in healthy teeth and teeth with pulpal diseases.

### *Exclusion Criteria*

Animal studies, Ex Vivo and in vitro studies, case reports, case series.

### *Search Strategy*

For identification of articles, search strategy was formulated by combining MeSH terms using the terms quoted in the articles and studies on Substance P. The search was carried out by two independent researchers (N.A and S.R). The search strategy was developed according to the inclusion and exclusion criteria of the study. The terms were searched in title, abstract and full text fields without any filter. The search included articles till 15th February,2022. The search was carried out in the following databases: MEDLINE via PubMed, Cochrane Library, Science Direct, Latin American and Caribbean Health Sciences (LILACS). Hand search in journals such as Journal of Endodontics and Google Scholar was done.

### *Study Selection and Data Collection*

The titles and abstracts of the articles found through the search were examined, if the article was repeated in different databases the duplicates were removed to avoid overlap of articles. If the abstract did not have sufficient information, full text was read and the articles were included or excluded. The study selection was done by two reviewers N.A and S.R. The eligible studies were shortlisted. The data was collected from these articles through customized tables based on Cochrane handbook 5.0.2 .

## RESULTS

### *Search results*

The search identified 67 publications among which 23 were duplicates and 29 were excluded after assessing the title. 15 Full text articles were

evaluated and 10 were excluded based on the inclusion and exclusion criteria. A total of 5 studies were included based on the previously mentioned criteria (Table 1).

The sample size ranged from 18 to 66, with a total of 173 participants in the 5 included studies(10,34–36). All the studies were performed in a University setting. One study measured Substance P level in GCF and four studies measured Substance P level in pulp tissue. Three studies used RadioimmunoAssay and two studies used Enzyme immunoAssay to quantify the level of Substance P in the collected samples. In three studies quantification of Substance P was done through RadioImmunoAssay and in two studies using Enzyme ImmunoAssay.

Awawdeh et al and Bowles et al compared substance P level between teeth with irreversible pulpitis and healthy teeth and found that Substance P was significantly increased in case of irreversible pulpitis. Bucheli et al compared SP level between teeth with irreversible pulpitis, pulp with induced inflammation and healthy teeth and reported that SP level was significantly increased in irreversible pulpitis when compared to pulp with induced inflammation and healthy teeth. Heidari et al compared the SP level between painful carious teeth and healthy teeth in the pediatric population and found that there was increased SP level in painful carious teeth. Sattari et al quantified and compared SP level between symptomatic, asymptomatic irreversible pulpitis and healthy teeth and reported significant increase in SP level in symptomatic irreversible pulpitis.

Quality assessment of the included studies was done using the Cochrane Collaboration tool for assessing the Risk of Bias for Diagnostic Studies. All the included studies had unclear risk of bias (Figure 1).

## DISCUSSION

Dental pulp is greatly innervated by sensory neurons containing neuropeptides such as Substance P, Calcitonin Gene Receptor Peptide (CRGP), Neurokinin A, Neurokinin B. In healthy teeth the presence of Substance P is attributed to

the regulation of blood supply in these teeth(37)(38)(37)(39)(22,40–42)(39).

Stimulation of these sensory afferent neurons leads to the release of neuropeptides causing development of neurogenic inflammation(43)(44–47)(43). The inflammation of the pulp is predominantly thought to be neurogenically mediated and contribute significantly to clinical signs and symptoms. There is a proportional increase in Substance P level in painful pulp compared to healthy pulp.

Substance P acts as a proinflammatory cytokine thereby evoking vascular changes and alters the permeability of dental pulp causing extravasation of plasma fluids and leading to edema(48,49)(22,40–42,50)(48,49)(51)(48,49)(48,49,52)(53)(48,49,52). These changes occur through the G-protein coupled receptor NK-1.

This systematic review revealed that there was significant increase in SP level in teeth with irreversible pulpitis when compared to healthy teeth. Symptomatic and painful teeth had greater levels of substance P than asymptomatic teeth. Substance P could be positively correlated with the pain experienced by the patient.

Substance P level can be used as a diagnostic tool in determining the inflammatory conditions of the pulp. It can also be used to determine and correlate the pain experienced by the patient and the efficacy of the endodontic procedures.

## CONCLUSION

SP, NKA, and CGRP are eminent neurotransmitters in the propagation of moderate to severe pain signals and are increased in case of pupal disease. Substance P is significantly increased in diseased pulpal conditions when compared to healthy and intact teeth.

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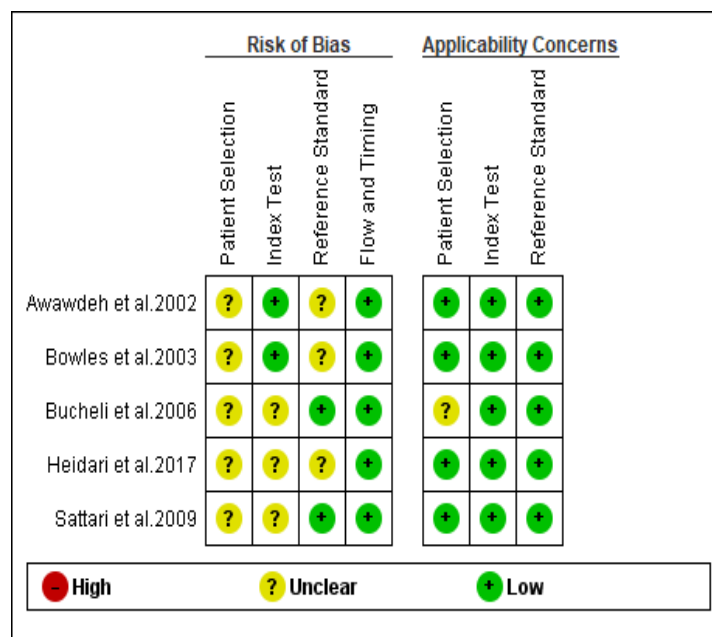
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**TABLE 1: Characteristics Of Included Articles**

S.No	Author	Sample size	Diseased Pulpal Condition	Comparison	Sample Examined	Method used for Analysis	Results	Outcome
1	Awadhet al.2002	n=66 (11-71 years)	Irreversible pulpitis (n=46)	Healthy teeth (n=20)	Pulp tissue	Radio-Immuno Assay	SP Level (ngg1) Pain- 3.6±2.8 Non-painful- 2.0±1.6 p=0.018	SP level significantly increased in irreversible pulpitis compared to healthy teeth
2	Bowles et al. 2003	n=21	Irreversible pulpitis (n=16)	Healthy Teeth (n=8)	Pulp tissue	Radio-immuno Assay	SP Level (pM) Inflamed pulp- 147.7±34.0 Normal pulp- 18.2±6.2 p=0.001	SP level significantly increased in irreversible pulpitis compared to healthy teeth
3	Bucheli et al.2006	n=18 (19-40 years)	Irreversible pulpitis (n=6) Pulp with induced inflammation (n=6)	Healthy pulp (n=6)	Pulp tissue	Radio-Immuno Assay	SP level Healthy pulp= 0.33±0.2 Pulp with induced inflammation=2 2.98±9.5 Irreversible pulpitis= 154.37±52.1	SP level Significantly increased in Irreversible pulpitis compared to Pulp with induced inflammation and healthy teeth

4	Sattari et al.2009	n=45 (13-46 years)	Asymptomatic Irreversible pulpitis (n=20) Symptomatic irreversible pulpitis (n=20)	Healthy teeth (n=5)	Pulp tissue	Enzyme-Immunoassay	p<0.0001 SP level in pg/mg Healthy pulp= 0.39±0.5 Asymptomatic Irreversible pulpitis= 148.5±42.4 Symptomatic Irreversible pulpitis= 178.7±46.6 p<0.001	SP level increased significantly in symptomatic and asymptomatic pulpitis when compared to healthy teeth
5	Heidari et al.2016	n=20 (7-12 years)	Painful decayed tooth	Healthy intact teeth	GCF	Enzyme Immunoassay	SP level in pg/ml Healthy teeth= 1.61±0.35 Painful decayed teeth= 2.65±0.56 p=0.0001	SP level significantly increased in Painful Decayed teeth when compared to healthy teeth



**FIGURE 1:** Risk of Bias Assessment using Cochrane Risk of Bias tool showing Unclear Risk of Bias for all the included studies.