

The nature of anterior knee pain following injection of hypertonic saline into the infrapatellar fat pad [☆]

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Abstract

The infrapatellar fat pad has been implicated as a possible source of anterior knee pain. This study examined the nature, distribution and time-course of experimentally induced pain in the infrapatellar fat pad. Hypertonic saline (5%) was injected into the medial fat pad of 11 healthy individuals with no history of knee pain. Severity of pain was assessed at rest and during activity using an 11 point numerical rating scale (NRS) at regular intervals over 15–30 min following injection. Participants described the size of the pain region from a series of different sized circles while the area and type of pain was established from a body chart and the McGill pain questionnaire. The effect of pain on temperature-pain threshold and sensory thresholds of the anterior knee was assessed. Participants generally reported a deep aching pain that peaked in severity around 3 min and gradually declined over 15 min. Pain levels were not altered by clinical manoeuvres designed to impinge the fat pad. The size of the pain region was related to pain intensity. Pain was most commonly felt in the region of the fat pad medial to the patella, although some individuals reported proximal referred pain as far as the groin region. Thermal and sensory thresholds were not altered at a region close to the injection site during the experimental pain. These results suggest that nociceptive stimulation of the infrapatellar fat pad may cause anterior knee pain that is not necessarily confined locally particularly if pain is severe. This has implications for the investigation of pathological structures in patients presenting clinically with anterior knee pain and provides an experimental model of anterior knee pain.

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Introduction

Multiple anatomical structures may be capable of producing anterior knee pain. These include the medial and lateral retinaculum, the patellar subchondral bone, the anterior synovium, the joint capsule, the patellar tendon and the infrapatellar fat pad. However, little research has investigated the pattern of pain referral produced by nociceptive irritation of these structures. Identification of potential sources of pain and a description of pain patterns are important for more accurate diagnosis and treatment of anterior knee pain.

The infrapatellar fat pad is one possible source of pain by virtue of its anatomical location. It is intimately related to the anterior knee joint compartment and lies in a space that is intra-articular but extrasynovial. It is bordered by the patellar tendon anteriorly, the inferior pole of the patella superiorly, the anterior horns of the menisci inferiorly, and the femoral condyles and intercondylar notch posteriorly [4]. Although the size and volume of the fat pad varies considerably between individuals, it consists of fascicles lying lateral and medial to the patellar tendon and a central portion behind the tendon. The fat pad is highly vascular with its blood supply originating from the synovial membrane [14]. Its nerve supply is primarily derived from the posterior articular nerve, a branch of the posterior tibial nerve [12].

Since Hoffa's first report in 1904 [9], there has been controversy about the role of the fat pad in clinical presentations of anterior knee pain and whether

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pathology of this structure is primary or secondary to other knee joint pathology [4]. Dye et al. [5] examined the pain perception resulting from instrumented arthroscopic palpation of internal components of the human knee without intra-articular anaesthesia. They found the fat pad to be one of the most pain-sensitive structures. The evoked pain was severe and could be accurately localised. Nerve fibres that are sensitive to substance-P (a peptide that activates nociceptors) have been found in the fat pad and are more prevalent in those with anterior knee pain compared with patients undergoing anterior cruciate ligament surgery or with knee joint osteoarthritis [20,21]. Surgical excision and injection of local anaesthetic and/or steroid into the fat pad have been reported to alleviate pain in some cases of anterior knee pain [3,4,19]. These findings suggest that the fat pad may be a potential source of symptoms in some individuals. Clinically, irritation of the fat pad has been argued to produce anterior knee pain that is aggravated by activities that compress the fat pad, including extremes of knee extension and loaded flexion such as squatting or ascending and descending stairs [3]. However, there is little information about the exact distribution and nature of pain that may arise if the fat pad is irritated as it is difficult to confirm that the nociceptive stimulus is confined to this structure.

Experimental pain models using healthy volunteers provide further insight into the nature of pain production from specific anatomical structures and allow controlled investigation of the effects of pain on various physiological parameters. Injection of hypertonic saline is a well-accepted, efficient and safe method to induce pain that has similar qualities to clinical musculoskeletal pain [1,11]. Hypertonic saline produces a continuous pain that rises rapidly to a maximum and subsides more slowly over a period of time, leaving no undesirable side effects. Animal experiments have shown that hypertonic saline in muscle induces firing in a large population of group III and IV nociceptive afferents [13,17]. The technique has been used primarily for intramuscular and intra-articular investigations. It has not been previously described for injection into other tissues or in local structures around the knee joint.

There is little research describing the pain patterns produced by irritation of anterior knee structures. The primary aim of this experiment was to describe the nature, distribution and time-course of symptoms resulting from injection of hypertonic saline into the infrapatellar fat pad in individuals with no history of knee pain. Sensory and thermal pain thresholds were also measured to assess the effect of phasic pain on low and high threshold cutaneous receptors over the patella. A secondary aim was to evaluate this experimental technique as a suitable model for further studies investigating the effects of anterior knee pain on neuromotor function.

Methods

Participants

Eleven (9 females, 2 males) healthy individuals were recruited from the staff and students of the University of Queensland and from professional colleagues. Individuals were excluded if they reported any history of lower limb pathology or injury to or pain in the tested knee for which treatment was sought or which interfered with function for more than one week. The mean (SD) age, height and weight of the participants was 34.4 (7.1) years, 167.2 (8.3) cm and 62.5 (13.0) kg respectively. The study was approved by the Institutional Ethics Committee and participants provided written informed consent.

Procedure

Saline injections

All injections were made into the medial fat pad region using a 25-gauge needle (Fig. 1). Prior to the saline injections, 0.05 ml of lignocaine (lidocaine 1%, Astra, Sweden) was injected subcutaneously to minimize cutaneous sensation. The needle was inserted at a 10° angle to a depth of ≈2 mm. Sterile hypertonic saline (5%, 0.20–0.25 ml, Astra, Sweden) was then injected into the same site at an angle of 45° in a superolateral direction. The needle was inserted to a depth of ≈10 mm. Pilot trials were conducted using different volumes (0.1–0.5 ml) and concentrations of hypertonic saline (5–10%) to determine the appropriate dose. The dose used was selected as it achieved the required pain intensity (VAS ~5) in the majority of subjects.

To confirm that the pain was due to chemical irritation of the fat pad rather than the mechanical effects of the injection, three participants also received an injection of isotonic saline (0.9%, Astra, Sweden) in the opposite knee. The participants and the tester administering the injection were blinded to each injection and were told that one or both might be painful. Both injections were aimed at the same location. For the isotonic saline, a 0.25 ml bolus was injected and the same measurements as for the hypertonic saline were taken following injection.

Pain measurement

Participants were asked to verbally indicate the severity of their pain using an eleven point numerical rating scale (NRS) anchored with the descriptors 'no pain' and 'worst pain'. Pain severity was measured in sitting at rest every 30 s after injection of hypertonic saline and during a step-up and a step-down from a 30-cm box every minute. Prior to the injection and at 2 min following injection, pain severity was also assessed during a passive extension overpressure performed by one of the testers and during a static quadriceps contraction.

Every 30 s, participants were asked to indicate the size of the area of knee pain from a diagram depicting a series of 10 circles increasing in size from 1 to 10 cm in diameter. The area of pain was determined

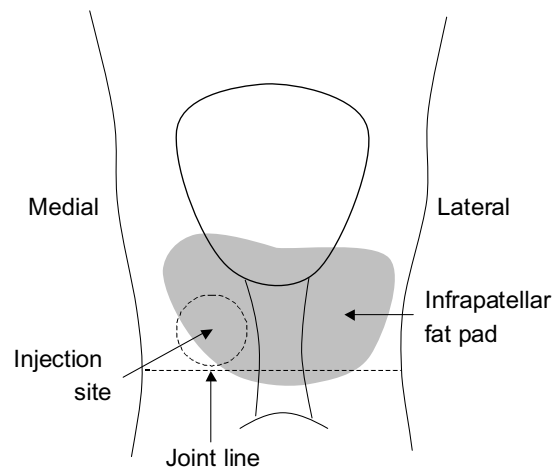


Fig. 1. Injection site into the medial fat pad.

from a knee body chart completed by the participant at 5-min intervals commencing at 2 min after injection. The quality of pain was assessed by the McGill pain questionnaire (MPQ) at the conclusion of the study. Pain rating indices based on rank values of the word descriptors were calculated [15]. Baseline measurements were taken to ensure there was no pain prior to injection.

Thermal pain and sensory threshold measurements

Sensory threshold and thermal-pain threshold were assessed on three occasions: at baseline, 3 min after injection of hypertonic saline (when pain was present), and at the conclusion of testing when the participant was painfree. Sensory testing preceded thermal-pain testing. Both tests were performed at the centre of the patella and with the participants' eyes closed.

The von Frey aesthesiometer (Somedic AB, Sweden) consisting of a set of filaments of increasing diameter was used to detect the threshold for sensation. The stimulus was increased in a stepwise fashion and the lowest stimulus at which the participant reported sensation was considered the sensory threshold.

A Thermostest Unit (Somedic AB, Sweden) was used to measure thermal pain threshold. This unit allowed a gradually increasing heat stimulus to be applied via a Peltier thermode. The unit was preset with a starting point of 30 °C increasing at a constant rate of 1 °C/s. The participant depressed a switch once they perceived that the sensation had changed from heat to pain and the temperature then returned to baseline. Two to three measures were taken at each assessment point and the mean of these measures was considered to be the thermal-pain threshold.

Magnetic resonance imaging

To assess the extent of infiltration of the saline into the fat pad, a MRI scan was performed in one participant. Immediately following an injection of 0.25 ml of isotonic saline, the participant was scanned in the supine position. The MR images were obtained with a superconducting 1.5 T MR imaging system (Magnetom Vision; Siemens, Erlangen, Germany) using a standard CP extremity coil. The participant was scanned with a fast STIR sequence in the coronal and axial planes. Imaging parameters were as follows, 3586/60/150 (TR/TE/TI), matrix 220×256 with 7/8 rectangular FOV to yield a 0.64×0.63 mm pixel size, FOV 160 mm, 2 acquisitions, 50% phase oversampling, and 5 mm slice thickness. The imaging data were reviewed on the MR monitor and printed for subsequent evaluation.

Statistical analysis

Descriptive statistics were calculated to assess the time-course of changes in pain severity and distribution. Non-parametric Friedmans tests were conducted to compare the temperature and pressure thresholds across the three time points. The correlation between pain severity and pain area over time was assessed using Spearman's rho.

Results

Severity of knee pain

All participants experienced pain following injection of hypertonic saline. Severity of pain increased rapidly and peaked at ≈ 3 min when the average pain level reported on the NRS was 5.8 but ranged from 2 to 10 (Fig. 2A). Average pain levels remained above 5 from 1 to 5.5 min. After this time, pain levels gradually declined and the majority of individuals were painfree by 15 min. Two individuals reported mild pain of 0.5 until 30 min after the injection. One individual was aware of a very slight burning sensation on the medial aspect of the knee that lasted for 3 days.

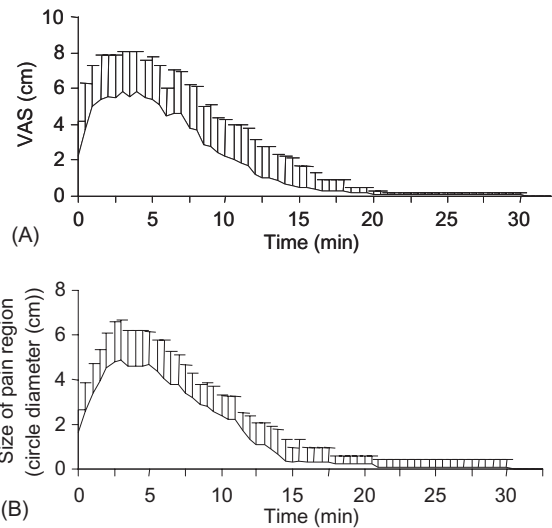


Fig. 2. (A) Time-course of pain severity during the experiment as measured on an 11 point numerical scale (NRS) every 30 s following injection of hypertonic saline. Results are expressed as the mean (SD). (B) Time-course of changes in the size of the pain region as measured every 30 s following injection of hypertonic saline. Results are expressed as the mean (SD).

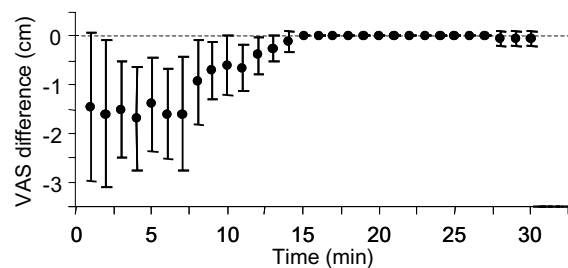


Fig. 3. Difference in level of pain during a step-up compared with the level of pain at rest across each time point following injection of hypertonic saline expressed as the mean (SD).

Stepping up or down from a step was associated with either no change in resting pain levels or a slight reduction in pain at all time points (Fig. 3). This reduction in pain with stepping was most apparent in the first 7 min. There was no difference in pain levels between step-up or step-down.

Severity of knee pain was generally unaltered by either passive extension with overpressure or a static quadriceps contraction at 2 min. The change in pain reported on the NRS with passive overpressure ranged from a 0.5 increase to a 3.5 decrease with the mean (SD) of -1.1 (1.2). The change in pain with static quadriceps contraction ranged from an increase by 0.5 to a decrease by 2.0 with a mean (SD) of -0.6 (0.9).

Size of pain region

The size of the pain region (Fig. 2B) showed a similar time-course to the severity of pain. Immediately

following injection, individuals reported the size of the pain region to be ~2 cm in diameter. This increased to a peak with a diameter of around 5 cm at 3 min. The size of the pain region gradually declined over time as pain severity decreased with a correlation of $r = 0.99$ ($p < 0.001$) between the two measures.

Distribution of pain

The distribution of pain at 2, 7 and 12 min is summarised in Fig. 4. Pain was perceived by at least one individual in all regions of the anterior knee except the lateral thigh above the lateral joint line (Region 2). At all time points, the most commonly reported sites of pain were the medial fat pad region (Region 5), the infero-medial retropatellar region (Region 9) and the patellar tendon (Region 4).

Three individuals (27%) described pain referral to the thigh. Of these, two felt pain extending from the knee into the medial and central thigh region up to the mid level and one felt pain in the groin.

Quality of knee pain

Using the MPQ, all participants described the pain as aching, 45% as throbbing, 37% as spreading and 27% as nagging. All participants chose one or more words to describe pain in the sensory categories, one participant (9%) chose a word in the affective categories, and six participants (45%) chose words in the evaluative and in

the miscellaneous categories. The overall pain rating index was 10.9 (range 7–18). For the individual pain categories, the rating index was 8.1 for the sensory, 0.09 for the affective, 2.8 for the evaluative and 2.8 for the miscellaneous category. The overall number of words chosen was 4.5 (range 3–8). The referred pain felt by the three participants was described as a dull ache by one and as a burning/heat by two.

Temperature and sensory thresholds

The mean (SD) sensory thresholds were 7.1 (1.6) for the baseline measurements, 7.0 (2.5) for the measurements 3 min after injection of hypertonic saline when participants were experiencing pain and 7.4 (2.6) for the measurements at the conclusion of the study when they were painfree. There was no significant difference in pressure thresholds across the three time-points.

The mean (SD) temperature thresholds were 41.0° (3.1°) for the baseline measurements, 41.1° (3.6°) for measurements 3 min after injection of hypertonic saline when participants were experiencing pain and 41.0° (3.6°) for the measurements at the conclusion of the study when painfree. There was no significant difference in temperature thresholds across the three time-points.

Isotonic saline injection

Immediately following injection of isotonic saline, one participant reported no pain and the other two reported a pain level of 0.5 and 4 on the NRS. At 60 s, two participants were painfree and the other reported a pain level of 0.5 cm. By 90 s, all three participants were painfree.

The distribution of pain was localised to Region 5 (Fig. 4) at the injection site. There was no pain felt in the patellar tendon or retropatellar region, nor was there any referral of pain. The pain was described as a dull

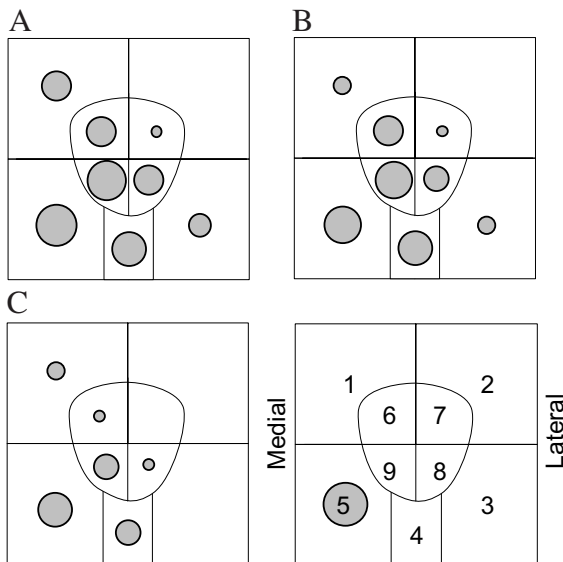


Fig. 4. Changes in pain distribution following injection of hypertonic saline displayed as a proportion of participants reporting pain in each region. The size of the circles represent the proportion of participants who reported pain in that region. (A) 2 min post-injection; (B) 7 min post-injection; (C) 12 min post-injection. The fourth panel shows the region number and the size of the reference circle indicating 100% of participants.

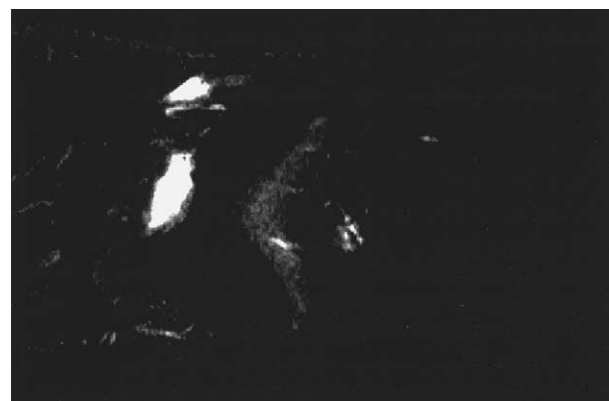


Fig. 5. MRI scan showing region of hypertonic saline infiltration in the infrapatellar fat pad.

feeling by one participant and as a sharp feeling or pin prick by the other two.

Magnetic resonance imaging

MR imaging of the infrapatellar fat pad of one individual following injection of 0.25 ml of isotonic saline revealed that the fluid remained within a discrete area \approx 1 cm in size posterior to the patellar tendon and 1–1.5 cm below the inferior pole of the patellar (Fig. 5). There was no visible infiltration close to the region of the anterior synovium.

Discussion

This study shows that injection of 0.20–0.25 ml of 5% hypertonic saline into the medial infrapatellar fat pad produces moderate to severe pain in the anterior knee region of individuals with no history of knee pain. The effects appear to be due to chemical irritation of nociceptors within the fat pad by the hypertonic saline. Mechanical effects of the injection are less likely to explain the pain production as a similar volume of isotonic saline resulted in either no pain or minimal pain lasting less than 90 s. Similarly, skin pain due to activation of cutaneous nociceptors by saline leaking up through the needle track was eliminated by firstly anaesthetizing the skin. The MRI scan showed that the hypertonic saline was confined to the region of the fat pad and did not infiltrate to the joint capsule or patellar tendon. Thus the pain experience described by participants in our study is likely to be due to stimulation of fat pad nociceptors by the chemical irritant. This confirms that the fat pad is a potential source of anterior knee pain.

Participants reported variable pain severity with one participant recording a maximum pain of 2 on the NRS and another recording 10. This is not unexpected given the subjective nature of pain and the individual differences in fat pad size and volume [4]. On average, pain peaked around 5 on the NRS and remained at this level for \sim 5 min. Pain lasted more than 13 min in all participants. This confirms the pain sensitive nature of the fat pad described by Dye et al. [5].

The distribution of pain reported by participants showed consistent features together with individual variation. All described local pain in the region medial to the patellar tendon around the injection site. The pattern of pain referral varied with most also feeling pain in the inferomedial retropatellar region and behind the patellar tendon. This may correspond to the size of the fat pad which has been shown to differ between individuals. The fat pad usually consists of two large basal prominences lying on each side of the intercondylar notch with three to six alar projections emanating from each basal prominence [2]. The extent of the local pain may also

depend upon the infiltration of the hypertonic saline into the fat pad with the potential for slight variations in injection penetration between participants. However, the MRI scan revealed that the small amount of fluid injected was confined to a localised region in the mid-portion of the fat pad directly behind the patellar tendon.

More distant pain referral was noted by some individuals and this included referral to the superior patella as well as the thigh and groin region. The spread of pain was related to its severity with a greater pain region correlating with more severe pain. As pain subsided with time, the area of pain also decreased. This is consistent with pain seen in other clinical conditions. The pain distribution pattern indicates that the fat pad is a potential source of pain in patients presenting with anterior knee pain. Furthermore, it shows that fat pad irritation not only results in local pain but may produce pain at distant regions of the lower limb especially if the pain is severe.

The most frequent words used by participants to describe the pain were sensory descriptors that include temporal, spatial, pressure, thermal and other properties. ‘Aching’ was a word selected by all participants with other common descriptors being ‘throbbing’ and ‘nagging’. This appears to differ from experimentally induced muscle pain where words such as ‘taut’, ‘drilling’ and ‘tight’ are more frequent descriptors [8]. Thus pain originating from the infrapatellar fat pad may have a different quality to muscle pain. However, similar to induced muscle pain, we found little use of affective word descriptors, or words that encompass fear, tension and autonomic properties [11,18]. This may reflect the acute and experimental nature of the pain stimulus. In clinical pain conditions, mean pain rating index scores for the affective category have been found to be higher, around 2–3, compared with our score of 0.08 [15].

We failed to find sensory processing changes for high and lower threshold receptors at a region over the patella and close to the injection site with our experimental pain protocol. Other investigators have found variable cutaneous responses following intra-muscular hypertonic saline injection [6–8,11]. Graven-Neilsen et al. [8] failed to demonstrate muscular or subcutaneous hyperalgesia after saline-induced muscle pain per se. Instead they found a non-specific muscular hyperalgesia after infusion of both isotonic and hypertonic saline at the infusion site but not at a site 4 cm from the infusion site [8]. It was suggested that these results may have been due to sensitisation of peripheral nociceptors due to the general experimental intervention. These researchers also showed that somatosensory changes in experimentally induced referred pain areas may be modality-specific [7]. Thus one cannot exclude the possibility that other modalities not measured in our study may have shown changes related to acute pain or that changes may have occurred directly over the injection site. Nevertheless, our findings suggest that if this experi-

mental paradigm is used for future investigations of the effects of pain on neuromotor function, the confounding influence of concomitant changes in cutaneous sensibility may be minimal.

While we reproduced anterior knee pain with this experimental model, we did not replicate the changes associated with pathology. Various intrinsic pathologic entities have been described for the infrapatellar fat pad [10]. However, the condition first described by Hoffa [9] involved impingement of the fat pad between the patella and femoral condyle giving rise to inflammation, hypertrophy and fibrosis. Since this time it is thought that irritation of the fat pad may occur with a prior insult to the knee, either surgical or traumatic, or following repetitive microtrauma. This can lead to an acute inflammatory response with pain and swelling. A swollen fat pad is then more susceptible to repetitive impingement resulting in fat necrosis and subsequent replacement by a firm mass of fibrous tissue [16]. Clinical findings may involve localised tenderness and puffiness in the fat pad region with reproduction of pain on manoeuvres that impinge the fat pad such as quadriceps contraction and passive knee hyperextension [3]. These tests did not aggravate the pain produced by hypertonic saline injection in our study. This is not surprising as the small volume of fluid injected would have been unlikely to have changed the size of the fat pad and therefore would not mechanically induce pain that could be altered by clinical tests.

In summary, experimental approaches using healthy volunteers provide a unique opportunity to study the pain pattern arising from nociceptive stimulation of specific structures and the effects of standardised pain on neuromotor performance and physiological parameters. Hypertonic saline injected into the medial fat pad produced strong knee pain in regions similar to those in patients presenting with anterior knee pain and of similar quality. This confirms that irritation of the fat pad is a potential source of anterior knee pain and should be considered in the differential diagnosis.

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